The Natural History of Cognitive Functioning in People with Newly Diagnosed Epilepsy

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Abstract

Background

Many people with epilepsy (PWE) experience cognitive problems as a consequence of their epilepsy and its treatment. However, relatively few longitudinal studies have been conducted to investigate how these problems progress during the course of the disorder, particularly in those who are newly diagnosed. This research was undertaken in the context of a pragmatic, randomised, unblinded, parallel-group, clinical trial assessing the clinical and cost effectiveness of standard and new antiepileptic drugs (SANAD). This trial provided a *unique* opportunity to investigate the natural history of cognitive functioning in people with newly diagnosed epilepsy.

Methods

A total of 222 people with newly diagnosed epilepsy were assessed using a comprehensive neuropsychological test battery before they started antiepileptic drug treatment. One hundred and forty seven were re-assessed after 12 months and a further 50 were followed-up after a mean of five years. Their cognitive performance at baseline and 12 months was compared to a healthy volunteer group (n=87) recruited from the general population.

Results

After adjusting for age, sex and education, PWE were cognitively compromised at the time of diagnosis, especially on measures assessing memory and psychomotor speed. After 12 months, PWE had a different cognitive trajectory compared with the healthy volunteers that was characterised by a lower than expected performance. After five years, the majority of measures remained stable, although significant declines were noted for memory and psychomotor speed domains. Not all PWE were affected, however, with 54% demonstrating impairment at baseline and 38% experiencing cognitive decline at five year follow-up.

Conclusions

For a proportion of people with newly diagnosed epilepsy, cognitive impairments were identified at the beginning of their epilepsy and this may be followed by further cognitive decline. In an ideal world, people with new-onset epilepsy should be referred for neuropsychological assessment at the time of diagnosis so those at risk can be identified for appropriate intervention.

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Author's declaration

This thesis is the result of my own work. The material contained in the thesis, has not been presented, nor is currently being presented, either wholly or in part for any other degree or other qualification.

The research work was carried out as part of the Standard and New Antiepileptic Drugs (SANAD) trial (Marson *et al.*, 2007a, 2007b), which was a large multicentre randomised clinical trial assessing the clinical and cost-effectiveness of standard and new antiepileptic drugs. The Neuropsychology study, as part of SANAD, was originally designed by my supervisor, Professor Gus A Baker. The neuropsychological assessments, as part of this study, were carried out by research assistants employed to work on SANAD. The healthy volunteer group was recruited and assessed by myself, with the assistance of an undergraduate psychology student (Caroline Perischine). However, I was responsible for carrying out the majority of the assessments. The recruitment and assessment of the people with epilepsy into the follow-up study, was also undertaken by myself, with the assistance of a Trainee Clinical Psychologist (Dr Laura Purdy). Again, I was responsible for the carrying out the majority of the assessments.

I decided on the statistical approach for the analysis of the data and carried out all the statistical analyses. However, advice was sought from Dr Ruwanthi Kolamunnage-Dona at the Centre for Medical Statistics and Health Evaluation at the University of Liverpool. I was responsible for interpretation and writing-up of all the data.

Related publications

Journal articles

- Taylor J & Baker GA (in press). Newly diagnosed epilepsy: Cognitive outcome at five years. *Epilepsy & Behaviour* doi: 10.1016/j.yebeh.2010.05.007.

- Taylor J, Kolamunnage-Dona R, Marson AG, Smith PE, Aldenkamp AP, Baker GA (2010). Patients with epilepsy: cognitively compromised before the start of antiepileptic drug treatment? *Epilepsia* 51 (1): 48-56.

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- Aldenkamp AP, Taylor J, Baker GA (2008). Cognitive side-effects of antiepileptic drugs. In Engel Jr J & Pedley TA (Eds). *Epilepsy: A Comprehensive Textbook 2nd Edition*. Lipincott, Williams & Wilkins, Philadelphia *pp 2085-2092.*

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- Taylor J & Baker GA (2009). The natural history of cognitive functioning in patients with newly diagnosed epilepsy: The longer term impact of epilepsy and its treatment. *Epilepsia* 50 (Suppl 10): 144

- Taylor J (2009). The immediate impact of epilepsy and its treatment. *Epilepsia* 50 (Suppl 4): 39.

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Conference proceedings

Platform presentations

- Taylor J. The immediate impact of epilepsy and its treatment. 8th European Congress on Epileptology. Berlin, 21st-25th September 2008.

- Taylor J & Baker GA (on behalf of the SANAD group). The natural history of cognitive functioning in patients with epilepsy: The longer term impact of seizures and treatment. ILAE UK Chapter Annual Scientific Meeting. Dundee, 9th-11th July 2008.

- Taylor J & Baker GA (on behalf of the SANAD group). Natural history of cognitive impairment in newly diagnosed epilepsy: The beginning. 27th International Epilepsy Congress. Singapore, 8th-12th July 2007.

Poster presentations

- Taylor J & Baker GA (on behalf of the SANAD group). The natural history of cognitive functioning in patients with epilepsy: The longer term impact of seizures and treatment. 28th International Epilepsy Congress. Budapest, 28th June-2nd July 2009.

- Taylor J & Baker GA (on behalf of the SANAD group). Patients with epilepsy: cognitively compromised before the start of antiepileptic drug treatment? Epilepsy Research UK International Expert Workshop. Oxford, 6th-8th April 2008.

- Taylor J & Baker GA (on behalf of the SANAD group). Natural history of cognitive impairment in epilepsy: The impact of seizures and treatment on memory and psychomotor functioning. 1st North American Regional Epilepsy Congress. San Diego 1st-5th December 2006.

- Taylor J & Baker GA (on behalf of the SANAD group). Natural history of cognitive impairment in epilepsy: The immediate impact of treatment. 7th European Congress on Epileptology. Helsinki, 2nd-6th July 2006.

Awards related to the research

- Best abstract award at the ILAE UK Chapter scientific meeting, July 2008

- Epilepsy Action Research Prize 2006

List of abbreviations

ABNAS	Aldenkamp-Baker Neuropsychological Assessment Schedule
AED	Antiepileptic Drug
AMIPB	Adult Memory and Information Processing Battery
ANOVA	Analysis of Variance
BCRT	Binary Choice Reaction Time
CBZ	Carbamazepine
CI	Confidence Intervals
CMHSE	Centre for Medical Statistics and Health Evaluation
CNS	Central Nervous System
CPS	Complex Partial Seizures
CT	Computed Tomography
CVST	Computerised Visual Search Task
CWE	Children with Epilepsy
EEG	Electroencephalogram
EXM	Euthosuximide
FBM	Felbamate
fMRI	Functional Magnetic Resonance Imaging
FSIQ	Full Scale IQ
GABA	Gamma-aminobutyric Acid
GBP	Gabapentin
GTCS	Generalised Tonic-Clonic Seizures
IBE	International Bureau for Epilepsy
ILAE	International League Against Epilepsy
IQR	Interquartile Range
ISC	Inadequate Seizure Control
LEV	Levetiracetam
LTG	Lamotrigine
MRI	Magnetic Resonance Imaging
MTLE	Mesial Temporal Lobe Epilepsy
OR	Odds Ratio
OXC	Oxcarbazepine
PB	Phenobarbital
PBO	Placebo
PGB	Pregabalin
PHT	Phenytoin
PIQ	Performance IQ
POMS	Profile of Mood States
PRM	Primidone
PWE	People with Epilepsy
QOL	Quality of Life
RAVLT	Rey Auditory Verbal Learning Test
RCI	Reliable Change Index
RCT	Randomised Clinical Trial
RT	Reaction Time
RUF	Rufinamide
SANAD	Standard and New Antiepileptic Drugs
SD	Standard Deviation
SE	Status Epilepticus
SMR	Standardised Mortality Ratio
SPSS	Statistical Package for Social Sciences
SRBs	Standardised Regression-Based Change Scores
SUDEP	Sudden Unexpected Death in Epilepsy
TCI	Transitory Cognitive Impairment
TEA	Transient Epileptic Amnesia
TGB	Tiagabine
TLE	Temporal Lobe Epilepsy
TPM	Topiramate
UAE	Unacceptable Adverse Events
VGB	Vigabatrin
VIQ	Verbal IQ
VNS	Vagal Nerve Stimulation
VPA	Sodium Valproate
VRT	Visual Reaction Time
WAIS (-R)	Wechsler Adult Intelligence Scale (-Revised)
WMS (-R)	Wechsler Memory Scale (-Revised)

All abbreviations are listed here unless the abbreviation is well known (e.g. UK, NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables, in which case, the abbreviation is defined in the figure legend or at the end of the table.

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Chapter 1 Introduction

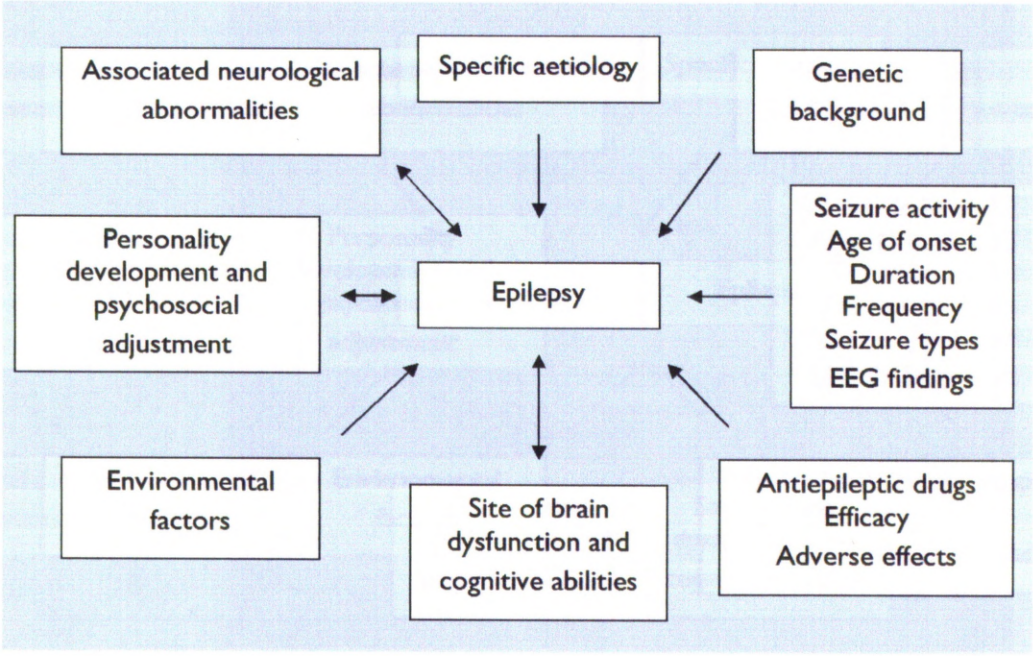
This chapter will briefly introduce the main issues that will be explored in this thesis and provide a short summary of its structure.

Epilepsy is one of the most common neurological conditions, affecting approximately 50 million people worldwide and 450 000 people in the United Kingdom. Around 3.5 million people are diagnosed with epilepsy every year. The majority of these will be managed with antiepileptic drugs (AEDs), which aim to control seizures with minimal adverse effects. The majority of people will become seizure free, although approximately 20-40% will continue to have seizures despite AED treatment. Chapter 2 will provide an overview of epilepsy and its management.

As illustrated in Figure 1.1, epilepsy is '*more than seizures*' having impacts on multiple aspects of an individual's life (Engel, Jr. & Pedley, 2008). The International League Against Epilepsy (ILAE) is recognising this in a move towards a new definition of epilepsy that encompasses its neurobiological, cognitive, psychological and social consequences (Fisher *et al.*, 2005).

This thesis will focus specifically on the effects of epilepsy on cognitive functioning. Cognitive functioning incorporates higher-order processes such as perception, attention, memory and learning, thinking, language, planning and problem-solving. These abilities allow us to process information, which enable us to interact with the world and other people. As cognitive difficulties can affect our social relationships, psychological well-being and quality of life, this area is worthy of significant investigation.

Figure 1.1: The multiple, interacting factors that contribute to the experience of epilepsy for an individual patient (taken from Engel, Jr. & Pedley, 2008)



Chapter 3 will review the substantial body of literature that has investigated the nature and cause of cognitive impairments in people with epilepsy. Several factors have been identified that contribute to the maintenance and development of cognitive dysfunction. These include the effects of the underlying aetiology; the effects of recurrent seizures, the side effects of antiepileptic drug treatment and psychosocial issues. Whilst a lot of attention has concentrated on the causes of cognitive impairment, particularly, the effects of antiepileptic drug treatment, Chapter 4 will illustrate the recent interest in determining *when* and *how* these impairments develop during the course of the disorder. A number of studies have suggested that people with epilepsy are already cognitively compromised at the time of diagnosis, before the start of antiepileptic drug medication. However, there is a lack of prospective longitudinal studies assessing whether these impairments get worse with the additional impact of seizures and treatment.

This thesis will explore the natural history[1] of cognitive functioning in people with newly diagnosed epilepsy by conducting a prospective, longitudinal study, as part of a larger, pragmatic, randomised clinical trial [Standard and New Antiepileptic Drugs (SANAD) trial (Marson *et al.*, 2007a, 2007b)]. The methods employed will be detailed in Chapter 5. A series of analyses will be undertaken that aim:

- To compare the cognitive profile of healthy volunteers with people with newly diagnosed epilepsy, before the administration of antiepileptic drug medication (Chapter 6)
- To compare the cognitive trajectories of people with newly diagnosed epilepsy and healthy volunteers over the first 12 months after starting AED treatment (Chapter 7)
- To document the longer term impact (3-8 years) of epilepsy and its treatment on cognitive functioning in people with newly diagnosed epilepsy (Chapter 8)

A discussion of the results and how they contribute to our understanding of the consequences of newly diagnosed epilepsy will be provided in Chapter 9. This chapter will also summarise the clinical implications and recommendations for future research.

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[1] The term 'natural history' implies the course of a disorder from onset without intervention until it resolves or death (Berg, 2008). However, in industrialised countries, most people are treated with antiepileptic drugs at the time of diagnosis (Kwan & Sander, 2004). A 'true natural history' may only be possible in the developing world, where in some countries (e.g. Pakistan and the Philippines), 94% of people with active epilepsy are not receiving treatment (Shorvon, 2009). For the purposes of this thesis, 'natural history' will refer to the course of cognitive functioning in those treated with AEDs. This approach has been adopted by other authors e.g. Hermann *et al.* (2006a, 2008a) who have referred to the 'natural history' of neuropsychological abnormalities and neurobehavioural comorbidities in people with epilepsy, and Seidenberg *et al.* (2007) who have used the term the 'natural course' of epilepsy, to mean without intervening surgery.

Chapter 2 Epilepsy and its treatment

2.1 Overview of the chapter

This chapter will provide a brief overview of epilepsy and its treatment. Epilepsy and epileptic seizures will be defined and the current classifications of epilepsy and epilepsy syndromes will be described. The incidence and prevalence will be reported and the causes of epilepsy will be discussed, as well as how a diagnosis of epilepsy is formed. There will be an overview of the history of epilepsy treatments from ancient remedies to modern day antiepileptic drugs. The current AEDs in clinical use and their indication will be provided. Treatment with AEDs is currently the first line approach in the management of epilepsy but other alternative treatments, such as, epilepsy surgery, vagal nerve stimulation, the ketogenic diet and psychological interventions will be reviewed.

2.2 Epilepsy

2.2.1 Definition of epilepsy

Traditionally, epilepsy has been defined as '*a chronic disorder characterised by recurrent epileptic seizures*' (Gastaut, 1973). An epileptic seizure is '*a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain*' (Fisher *et al.*, 2005). Epilepsy is not a single disease but encompasses a variety of heterogeneous disorders that are all symptoms of an underlying neurological disorder (Stokes *et al.*, 2004).

There is now recognition that epilepsy is more than a clinical condition, with consequences on an individual's life that can be more debilitating than the seizures themselves. Therefore, the ILAE has moved towards a new definition that acknowledges these consequences. They have defined epilepsy as: '*a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social*

consequences of the condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure' (Fisher *et al.*, 2005).

2.2.2 Classification of seizures

There are many different types of seizures. Their clinical presentation generally depends on the location of the seizure in the brain and how the seizure spreads throughout the cerebral cortex. The ILAE 1981 classification of seizure types, as shown in Table 2.1, is the most commonly used and adopted classification. It divides seizures into:

- **Partial seizures** where seizure activity originates from part of one cerebral hemisphere;
- **Generalised seizures** where seizure onset involves both hemispheres. Consciousness is usually altered due to the extensive cortical involvement.

Partial seizures are subdivided into three types:

- **Simple partial seizures** do not have an alteration of consciousness. They usually only last for a few seconds. The seizures originate from a localised brain area and the sensations experienced (e.g. jerking, spasm or burning), depend on the localisation of the seizure. For example, simple partial seizures with motor signs, involve the motor cortex.
- **Complex partial seizures** involve alterations of consciousness. Before a complex partial seizure, an individual may experience an aura (a simple partial seizure) that acts as a warning. During the seizure, an individual may demonstrate automatisms (automatic behaviours), for example, lip smacking, gestures or verbal utterances. They may appear awake but do not respond to verbal instructions or questions. These usually last for one to two minutes. The postictal period may last up to a few hours.
- **Either simple partial or complex partial seizures can evolve**, by spreading through neuronal networks, to generalised seizures, which may be generalised

tonic-clonic, tonic or clonic. These are known as secondarily generalised seizures.

Table 2.1: Classification of seizure types (taken from the Commission of the ILAE, 1981)

Partial (focal)	Simple partial (consciousness not impaired) • With motor signs • With somatosensory or special sensory symptoms (e.g. simple hallucinations) • With autonomic symptoms or signs (e.g. flushing) • With psychic symptoms (e.g. déjà vu)
	Complex partial seizures (with impairment of consciousness) • With simple partial onset followed by impairment of consciousness • With impairment of consciousness at onset
	Partial seizures evolving to secondarily generalised seizures (may be generalised tonic-clonic, tonic or clonic) • Simple partial seizures evolving to generalised seizures • Complex partial seizures evolving to generalised seizures • Simple partial seizures evolving to complex partial seizures evolving to generalised seizures
Generalised (convulsive or non-convulsive)	Absence seizures • Typical absence • Atypical absence Myoclonic seizures Clonic seizures Tonic seizures Tonic-clonic seizures Atonic seizures
Unclassified	Unclassified seizures

Generalised seizures are subdivided into six main types:

- **Absence seizures** (formerly 'petit mal' seizures) have a sudden onset and an abrupt end. During the absence, an individual may demonstrate a vacant/staring appearance that lasts for a few seconds. There is no postictal confusion.
- **Tonic-clonic seizures** (formerly 'grand mal' seizures) involve sudden contraction of the muscles, which is followed by clonic convulsive movements. These last no more than two to three minutes. They may be accompanied by tongue biting and

urinary incontinence. Afterwards, an individual may remain unconsciousness for a time or sleep deeply.

- **Clonic seizures** may occur on their own without the tonic phase (rhythmic muscle contractions).
- **Tonic seizures** may occur without the clonic phase (stiffening of muscles).
- **Myoclonic seizures** are characterised by single or multiple jerking movements. These can particularly occur on falling asleep or waking.
- **Atonic seizures** involve a loss of muscle tone. This can vary in severity from causing the head to drop or jaw to slacken to causing an individual to drop to the ground. These are sometimes known as drop attacks or astatic seizures.

Unclassified seizures are those that cannot be determined whether the seizure is generalised or partial with secondarily generalisation. About one third of seizures cannot be classified according to the ILAE classification (Shorvon, 2000).

In addition to these seizure types, clinicians distinguish unprovoked seizures from provoked seizures (or acute symptomatic seizures). Acute symptomatic seizures '*occur at the time of a systemic insult or in close temporal association with a documented brain insult*' (Beghi *et al.*, 2009). There is debate about whether these should be included in a diagnosis of epilepsy because they do not recur when the cause is removed.

Another important condition is status epilepticus (SE). Status epilepticus is either a single clinical seizure that lasts for more than 30 minutes or repeated tonic-clonic seizures over a period of more than 30 minutes without recovery of consciousness. However, urgent treatment should be sought after five minutes. SE can lead to anoxic brain damage and cognitive deterioration due to the cessation of respiration during the tonic phase of the seizure. Tonic-clonic SE is the most recognised but non-convulsive status may occur, such as absence or complex partial status.

Causes of epileptic seizures

Epileptic seizures may be caused by a number of factors and a number of seizure precipitants have been identified. These include stress; sleep deprivation and fatigue; sleep/wake cycle; alcohol and alcohol withdrawal; antiepileptic drug noncompliance; metabolic disturbances; toxins and drugs; exercise and the menstrual cycle (Shorvon, 2000, Jallon & Zifkin, 2008). Identifying seizure precipitants for an individual may help in treatment, for example, avoidance of situations that are known to trigger seizures, or psychological therapy to reduce stress, which may improve seizure control.

2.2.3 Classification of epilepsy syndromes

To supplement the classification of seizures, there is also a classification system for epilepsies and epilepsy syndromes. '*An epilepsy syndrome is an epileptic disorder characterised by a cluster of signs and symptoms customarily occurring together*' (Commission of the ILAE, 1989). These signs and symptoms include types of seizures; aetiology; age of onset; family history; other neurological signs and electroencephalogram (EEG) findings. Table 2.2 is the 1989 classification for epilepsies and epileptic syndromes from the Commission on Classification and Terminology of the ILAE (1989). The epilepsies are classified as to whether they are localisation-related (i.e. have partial-onset seizures) or generalised (i.e. have generalised seizures) and whether the underlying cause is idiopathic, symptomatic or cryptogenic. Idiopathic means the only cause is a possible hereditary disposition. Symptomatic is the result of a lesion or other identifiable underlying pathology. Cryptogenic is when the cause is unknown but is presumed to be symptomatic. With the advancing of imaging, many epilepsies that were previously cryptogenic can now be classified as symptomatic (Shorvon, 2000).

Table 2.2: Classification of the epilepsies and epileptic syndromes (Commission of the ILAE, 1989)

Localisation-related (focal, partial)	Idiopathic (with age-related onset)	• Benign childhood epilepsy with centrotemporal spikes • Childhood epilepsy with occipital paroxysms • Primary reading epilepsy
	Symptomatic	• Chronic progressive epilepsia partialis continua of childhood • Characterised by specific modes of precipitation (e.g. temporal lobe, frontal lobe, parietal lobe, occipital lobe, bi-and multilobar epilepsies)
	Cryptogenic	• Cryptogenic epilepsy
Generalised	Idiopathic (with age-related onset)	• Benign neonatal familial convulsions • Benign neonatal convulsions • Benign myoclonic epilepsy in infancy • Childhood absence epilepsy • Juvenile absence epilepsy • Juvenile myoclonic epilepsy • Epilepsy with GTCS on awakening • Other idiopathic generalised epilepsies • Epilepsies precipitated by specific modes of activation
	Cryptogenic or symptomatic	• West syndrome (infantile spasms) • Lennox-Gastaut syndrome • Epilepsy with myoclonic-astatic seizures • Epilepsy with myoclonic absences

	Symptomatic	• Non-specific aetiology
		  o Early myoclonic encephalopathy
		  o Early infantile epileptic encephalopathy with suppression burst
		• Specific syndromes
		  o Caused by malformations
		  o Proven or suspected inborn errors of metabolism
		• Other symptomatic generalised epilepsies

Undetermined (focal or generalised)	With both generalised and focal seizures	• Neonatal seizures • Severe myoclonic epilepsy in infancy • Epilepsy with continuous spike-waves during sleep • Acquired epileptic aphasia (Landau-Kleffner)
	Without unequivocal generalised or focal features	• Without unequivocal generalised or focal features
Special syndromes	Situation-related seizures	• Febrile convulsions • Isolated seizures or isolated status epilepticus • Seizures due to acute metabolic or toxic factors • Reflex epilepsy

Due to several criticisms of the classifications, and advancements in knowledge about epilepsy, there have been attempts to update them in 2001 and 2006. In 2001, the ILAE Task Force proposed a multi-axial diagnostic scheme for describing individual patients. They proposed that patients should be classified according to their ictal phenomenology; seizure type; syndrome; aetiology and optionally their degree of impairment (Engel, Jr., 2001). The diagnostic scheme was designed to help clinicians determine the diagnostic tests and treatment to be used in individual patients. However, the ILAE Task Force in 2006 reported that this proposal had not replaced the previous classifications and so the earlier versions should continue to be employed until a better classification has been devised (Engel, Jr., 2006). The classifications have been reviewed again in 2009 and a new classification has still not been proposed, although updates have been made to terminology and concepts. For example, syndromes should no longer be characterised as being generalised or focal (localisation-related), and the terms idiopathic, symptomatic and cryptogenic should be replaced by genetic, structural/metabolic and unknown (Berg *et al.*, 2010).

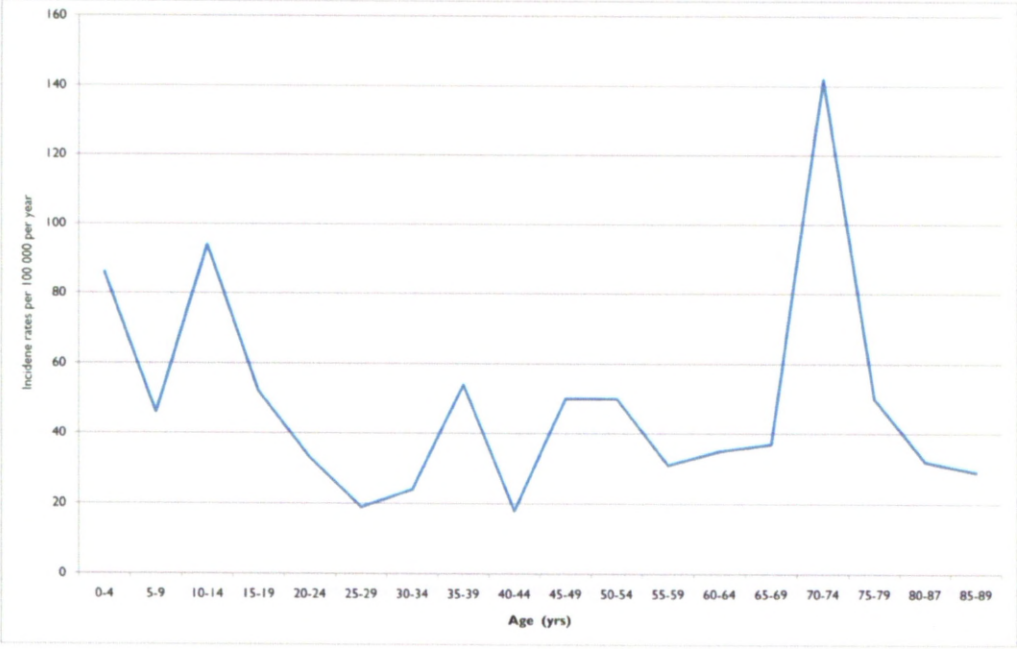
2.2.4 Incidence and prevalence

Epilepsy is the one of the most common neurological conditions. One in ten people will have at least one epileptic seizure in their lifetime and a third of these will go on to develop epilepsy (Engel, Jr. & Pedley, 2008). Approximately 50 million people have epilepsy worldwide (World Health Organisation, 2009) and approximately 450 000 people have epilepsy in the United Kingdom (Joint Epilepsy Council of the UK and Ireland, 2005). The prevalence of active epilepsy ranges between 4 and 10 per 1000 persons (Sander, 2003) and in the UK a prospective community-based study found a lifetime prevalence of active epilepsy of 4 per 1000 persons [95% Confidence Intervals (CI) 4, 5] (MacDonald *et al.*, 2000).

A meta-analysis of 40 incidence studies conducted worldwide between 1966 and 1999 found a median incidence rate of epilepsy of 47.4 cases per 100 000 per year (Kotsopoulos *et al.*, 2002). However, the incidence rate was higher in developing countries (e.g. industrialised countries median 43.4 per 100 000 per year vs. developing countries median 68.7 per 100 000 per year) (Kotsopoulos *et al.*, 2002). This is possibly the result of developing countries having poorer medical facilities; poorer general health; lower standard of living and more

infections of the central nervous system (CNS), such as tuberculosis and human immunodeficiency virus (HIV) (Bharucha *et al.*, 2009). In the UK, the incidence of epilepsy is 46 per 100 000 per year (95%CI 36, 60) (MacDonald *et al.*, 2000). The risk of an individual developing epilepsy in their lifetime is between 3 and 5% (Shorvon, 2000).

Figure 2.1: Age-specific incidence rates for epilepsy adjusted to the UK population (data from MacDonald et al., 2000)



The onset of epilepsy is more common in young children, particularly during the first few months, and older adults (see Figure 2.1). However, recent studies have shown that the incidence rate in children is decreasing while the incidence rate in those aged over 60 years is increasing (Kotsopoulos *et al.*, 2002, Sander, 2003). A decrease in childhood may be due to the adoption of healthier lifestyles by expectant mothers; improved antenatal and prenatal care, and enhanced immunisation programmes. This may lead to a reduction in neuronal migration defects, in birth hypoxia and in CNS viral infections, which may be involved in the development of epilepsy (Sander, 2003). The increase in older adults may be the result of a rise in the number of people who have had a history of a stroke, which is a risk factor for developing epilepsy (Sander, 2003, Banerjee & Hauser, 2008).

The incidence of epilepsy is higher in males than in females, although this is not always statistically significant (Banerjee & Hauser, 2008). In the meta-analysis by (Kotsopoulos *et al.*, 2002), the median incidence for males was 50.7 per 100 000 per year compared with 46.2 per 100 000 per year for females. Possible reasons for the difference are that males have a higher incidence of risk factors for epilepsy such as head injury, stroke and CNS infection (Kotsopoulos *et al.*, 2002).

2.2.5 Mortality of epilepsy

There is a higher risk of mortality in people with epilepsy. The standardised mortality ratio (SMR) is two to three times higher than the general population. The risk is increased in those who have chronic epilepsy, especially younger people, and those with symptomatic epilepsy (Sander, 2003). The cause of death may be related to the underlying aetiology; drowning; burns; aspiration; pneumonia; status epilepticus and suicide. There is evidence to suggest an increased risk of suicide in people with epilepsy compared to the general population (Bell & Sander, 2009). A recent meta-analysis has found an overall SMR for suicide in people with epilepsy of 3.3 (95%CI 2.8, 3.7). However, the risk is increased for those with a psychiatric co-morbidity, particularly an affective disorder (Bell *et al.*, 2009). Epilepsy-related deaths may also be accounted for by Sudden Unexpected Death in Epilepsy (SUDEP). SUDEP is '*sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, in which post mortem examination does not reveal toxological or anatomic cause of death*' (Nashef, 1997). The mechanisms that lead to SUDEP are unknown but risk factors include generalised tonic-clonic seizures; young age; uncontrolled epilepsy; learning disability; seizures occurring during sleep; unwitnessed seizures and poor adherence to antiepileptic drug treatment (Shorvon, 1997).

2.2.6 Causes of epilepsy

There are a wide range of underlying aetiologies for epilepsy, as shown in Table 2.3. However, specific aetiologies are usually only identified in approximately one third of people with newly diagnosed epilepsy (Banerjee & Hauser, 2008). In the UK National General

Practice Study of Epilepsy, 61% of people with newly diagnosed epilepsy, or suspected epileptic seizures, had no identifiable aetiology. However, vascular disease was the most common cause in 15% and cerebral tumour in 6% (Sander *et al.*, 1990).

Table 2.3: Aetiology of epilepsy (adapted from Shorvon, 2000)

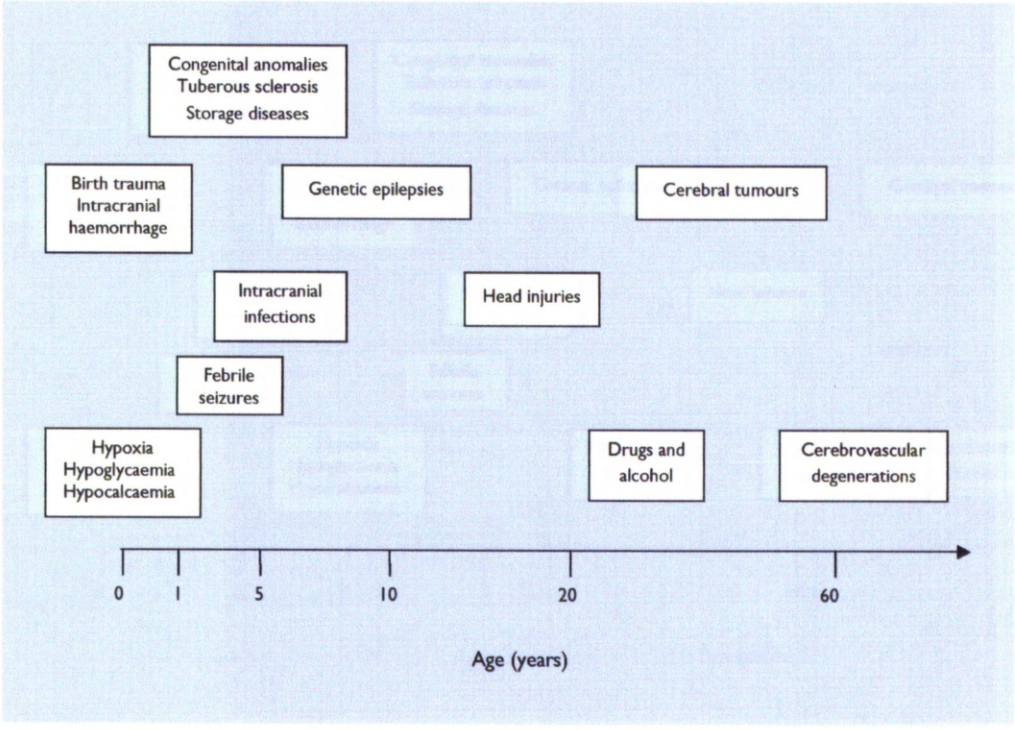
Inherited genetic conditions	• Genetic disorders causing epilepsy alone (e.g. juvenile myoclonic epilepsy, familial frontal lobe epilepsy)
	• Inherited conditions with other neurological manifestations
	  o DNA expansion syndromes (e.g. Down syndrome, Fragile X syndrome)
	  o Other inherited conditions with extrapyramidal features (e.g. Wilson's disease)
	  o Other inborn errors of metabolism (e.g. phenylketonuria, amino acid disorders)
	• Inherited metabolic disorders with intermittent disturbances (e.g. porphyria)
	• Neurocutaneous syndromes (e.g. tuberous sclerosis, neurofibromatosis)

Acquired or congenital disorders	• Vascular malformations (e.g. arteriovenous malformations, cavernous angiomas) • Hippocampal sclerosis • Cortical dysplasia/ dysgensis (e.g. focal cortical dysplasia, heterotopias) • Immunisation (e.g. diphtheria, tetanus and polio vaccine) • Infection (e.g. bacterial meningitis, viral encephalitis, cerebral abscess) • Cerebral tumours (e.g. oligodendrogliomas, meningiomas) • Post-traumatic epilepsy • Neurosurgery • Cerebrovascular disease (e.g. ischemic stroke, intracranial haemorrhage) • Antenatal or perinatal injury • Birth trauma (e.g. hypoxia, intracranial haemorrhage) • Alcohol/Drugs (e.g. alcohol withdrawal) • Toxic agents (e,g encephalopathy caused by lead poisoning) • Metabolic disorders (e.g. changes in glucose, calcium, potassium and magnesium) • Neurodegenerativce disorders (e.g. Alzheimer's Disease, Creutzfeldt-Jakob disease) • Other diseases (e.g. Coeliac disease, multiple sclerosis)

As shown in Figure 2.2, aetiologies often vary by age. In childhood, congenital, developmental and genetic conditions are often associated with the development of epilepsy. Head injuries, CNS infections and tumours are more likely to lead to epilepsy in adulthood and cerebrovascular disease is the most common risk factor for epilepsy in those aged over 60 years (Sander, 2003). Similarly, in the UK National General Practice Study of Epilepsy,

vascular disease was more common in those aged over 60 years (49%) and tumours in those aged 50-59 years (Sander *et al.*, 1990).

Figure 2.2: Aetiology of epilepsy at different ages (taken from Brodie et al., 2005)



2.2.7 Diagnosis of epilepsy

A diagnosis of epilepsy should be made by an epilepsy specialist (Stokes *et al.*, 2004). It is usually only made after the occurrence of at least two unprovoked seizures (Stein & Kanner, 2009). The diagnosis is based on clinical history and a detailed description of the events experienced by a patient, before, during and after a seizure. This description should be from the patient and if possible an eyewitness to the seizure. Electroencephalography (EEG) can be used to support the clinical diagnosis of epilepsy and help determine whether seizures are partial or generalised. However, standard or routine EEGs have variable sensitivity and specificity (Stokes *et al.*, 2004). Several studies have shown that the EEG may be abnormal in people without epilepsy and may also be normal in people with epilepsy (Fowle & Binnie,

2000). One study found that 48% of people with epilepsy had a normal EEG (Goodin & Aminoff, 1984). Structural neuroimaging, for example magnetic resonance imaging (MRI) and computed tomography (CT), can be used to identify structural abnormalities, such as tumours, vascular lesions, atrophy or stroke that may have caused the epilepsy. It is particularly important in those who present with partial-onset seizures and have adult-onset epilepsy (Stokes *et al.*, 2004).

2.3 Epilepsy treatment

Treatment with antiepileptic drugs is currently the first approach in the management of people with epilepsy. However, there is a long history of treatments for epilepsy, which will be briefly detailed below.

2.3.1 History of treatments for epilepsy

"There is scarcely a substance in the world capable of passing through the gullet of a man that has not at one time or another enjoyed the reputation of being an antiepileptic"

(Sieveking, taken from Scott, 1993)

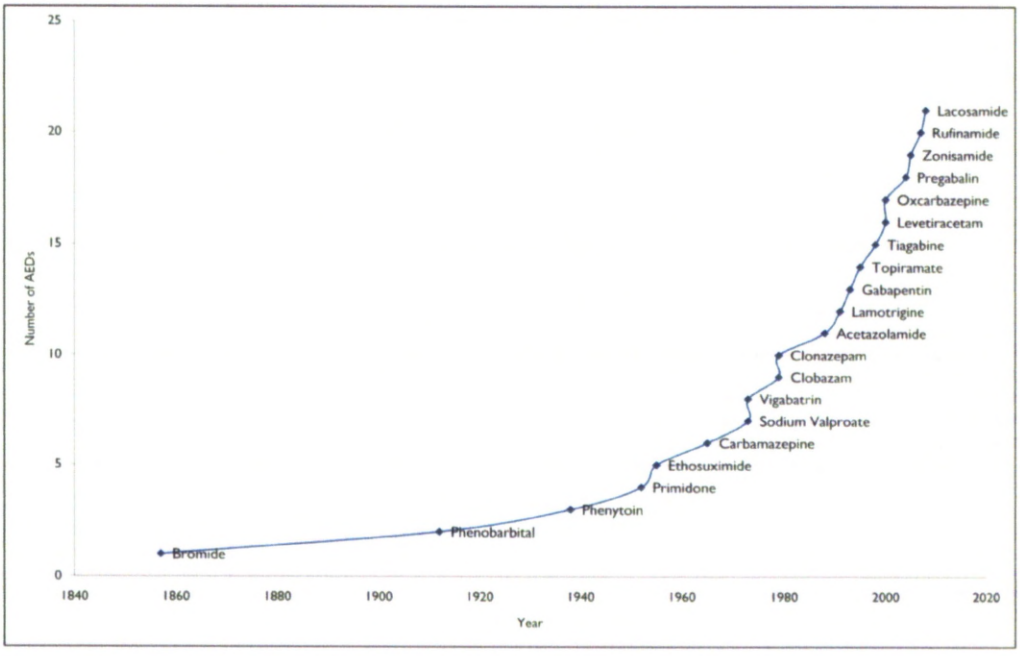
Throughout history, many different substances and techniques have been used in the treatment of people with epilepsy. Treatments have largely reflected the differing theories of causation. In Babylonian and Greek times, epilepsy was thought to be the result of possession by a demon or spirit (Reynolds, 2009). Therefore, treatments, such as exorcism, were largely based on mysticism and superstition (Haynes & Bennett, 1992). The Hippocratic School moved towards a physiological basis for the disorder and '*the brain being the seat of the disease*'. Treatment around this time included diet, exercise, sleep and a consideration of temperature and climate factors (Temkin, 1971). Herbal remedies included drinking vinegar and wormwood (Temkin, 1971) and ancient Indian medicinal treatments involved tree bark, sour milk curds, animal parts and even excrement (Scott, 1993).

In the Middle Ages, the idea that epilepsy was the result of supernatural causes was revived and exorcism remained a prevalent form of treatment. Superstitious and religious remedies continued to persist, such as the wearing of amulets of peony or stones, drinking blood, and pilgrimages to the prior of St Valentine, the patron saint of epilepsy (Temkin, 1971, Haynes & Bennett, 1992). During this time, potions contained powdered human skull, liver of vultures and mistletoe (Scott, 1993).

In the 19th Century, the idea of demonic possession began to fade, as the knowledge of anatomy and physiology increased. It was during the 1850s that the first anticonvulsant drug, potassium bromide was introduced by Sir Charles Locock. The use of bromides quickly became widespread. Around this time, barbituric acid was first synthesised but it was not until 1912 that the effectiveness of phenobarbital (PB) as an antiepileptic was recognised by Alfred Hauptman (Kwan & Brodie, 2004). Phenobarbital came into use quickly but the next major antiepileptic drug, phenytoin (PHT), was not introduced until the late 1930s by Merrit and Putman. The previous drugs had been discovered by chance but phenytoin was the first AED that resulted from a systematic study to identify new antiepileptic drugs by findings molecules that resembled phenobarbital (Daras *et al.*, 2008).

It was nearly 20 years later before carbamazepine (CBZ) was first synthesised in the search for more effective psychoactive drugs (Shorvon, 2009). But carbamazepine was not used as an antiepileptic until the early 1960s. Meanwhile, during the early 1950s, primidone (PRM) and euthosuximide (EXM) were licensed for use. At a similar time, the antiepileptic properties of sodium valproate (VPA) were discovered by chance. Sodium valproate was initially used an organic solvent in screening studies of new antiepileptic drugs. However, it was soon realised that it was the solvent, not the tested compounds, which was the effective antiepileptic agent. The first clinical trials of sodium valproate were undertaken in 1964. It was first marketed in France and then licensed for use in the UK in 1973.

Figure 2.3: Growth in the number of AEDs



During the 1960s and 1970s, more formalised assessments of AED efficacy and tolerability were required and so several compounds disappeared as they could not face the cost of rigorous testing (Scott, 1993, Glauser *et al.*, 2006). However, over the last two decades, there has been a huge growth in the number of AEDs, as shown in Figure 2.3. These have included lamotrigine (LTG), gabapentin (GBP), topiramate (TPM) and tiagabine (TGB) in the 1990s and levetiracetam (LEV), oxcarbazepine (OXC) and pregabalin (PGB), among other new developments in the 2000s. Their development and discovery has been the result of several different strategies including: random screening of numerous molecules with a wide range of chemical structures (e.g. felbamate[2]); testing structural analogues of known AEDs (e.g. oxcarbazepine) and modifying factors believed to facilitate epileptic activity [e.g. gabapentin and gamma-aminobutyric acid (GABA)] (Daras *et al.*, 2008).

[2] Felbamate (FBM) is not licensed for use in the United Kingdom. It is licensed for use in the United States but only in patients with severe epilepsy due to the risks of aplastic anaemia (Panayiotopoulos, 2007).

Treatment with AEDs

The goal of antiepileptic drug treatment is to prevent seizures with minimal side-effects. There are a number of AEDs currently licensed for use in the UK, as shown in Table 2.4. The choice of AED should be determined by seizure type; epilepsy syndrome; indication; childbearing potential; co-morbidity; preferences of the individual and/or carer; concomitant medication; presence of contraindications to the drug and potential adverse effects (Stokes *et al.,* 2004). The results of the recent SANAD trial suggest that lamotrigine may be a clinically cost-effective drug for those with partial-onset seizures (Marson *et al.*, 2007a). Valproate remains the most clinically effective drug for those with generalised or unclassified epilepsy (Marson *et al.*, 2007b). However, valproate is associated with teratogenic effects (e.g. Adab *et al.*, 2004) and so the question of which is the most appropriate drug for women of child-bearing age is a difficult issue.

Patients should be treated with a single drug (monotherapy) first and if that fails, either due to inadequate seizure control or unacceptable events, they should be treated with an alternative drug (Stokes *et al.*, 2004). Patients may be treated with more than two drugs (polytherapy) if monotherapy has not resulted in seizure freedom. However, this is associated with more side effects; pharmacokinetic interactions, increased risk of teratogenecity and more complex and intrusive AED regimen (Shorvon, 2000). Some have suggested that selecting a second drug that has a differing mechanism of action is a rational approach. However, others say that there is little evidence to suggest that this has an effect (Shorvon, 2000).

The mechanisms of action of several of the most commonly used AEDs and their adverse effect profiles are shown in Table 2.5. For many AEDs their mechanisms of action are still not fully understood and several have more than one mechanism of action (Perucca, 2005). Some work by blocking different ion channels in the brain, while others work by increasing the levels of GABA in the brain, which is the main inhibitory neurotransmitter. However, a discussion of the pharmacokinetics of AEDs is beyond the scope of this thesis.

Table 2.4: AEDs currently licensed for use in the UK and their indication (adapted from the Joint Formulary Committee, 2009)

Generation	AED	Indication
1st	Phenobarbital	• All forms of epilepsy except absence seizures
	Phenytoin	• All forms of epilepsy except absence seizures
	Primidone	• All forms of epilepsy except absence seizures
	Ethosuximide	• Absence seizures
	Carbamazepine	• Partial and secondary generalised tonic clonic seizures; primary generalised tonic-clonic seizures
	Sodium valproate	• All forms of epilepsy
2nd	Vigabatrin	• Adjunctive treatment of partial seizures with or without secondary generalisation not satisfactorily controlled with other AEDs; monotherapy for management of infantile spasms (West's syndrome)
	Clobazam	• Adjunctive therapy
	Clonazepam	• All forms of epilepsy
	Acetazolamide	• Treating epilepsy associated with menstruation; adjunctive therapy for tonic clonic and partial seizures; occasionally helpful in atypical absences and tonic clonic seizures
	Lamotrigine	• Monotherapy and adjunctive treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures; seizures associated with Lennox-Gastaut syndrome
	Gabapentin	• Monotherapy and adjunctive treatment of partial seizures with or without secondary generalisation
	Topiramate	• Monotherapy and adjunctive treatment of generalised tonic-clonic seizures or partial seizures with or without secondary generalisation; adjunctive treatment of seizures in Lennox-Gastaut syndrome
	Tiagabine	• Adjunctive treatment for partial seizures with or without secondary generalisation not satisfactorily controlled with other AEDs
	Levetiracetam	• Monotherapy and adjunctive treatment of partial seizures with or without secondary generalisation and for adjunctive therapy of myoclonic seizures and generalised tonic-clonic seizures
	Oxcarbazepine	• Monotherapy and adjunctive treatment of partial seizures with or without secondary generalised tonic-clonic seizures
	Pregabalin	• Adjunctive therapy for partial seizures with or without secondary generalisation
	Zonisamide	• Adjunctive therapy for partial seizures with or without secondary generalisation
3rd	Rufinamide	• Adjunctive treatment of seizures in Lennox-Gastaut syndrome
	Lacosamide	• Adjunctive therapy of partial seizures with or without secondary generalisation

Table 2.5: Mechanisms of action and common side effects of AEDs patients were taking during this research programme (adapted from the Joint Formulary Committee, 2009)

AED	Mechanism of action	Common side effects	Initial dose (mg)	Maintenance dose (mg)
Carbamazepine	Exact mechanism unknown but thought to work on sodium channels. May also work on monoamine, acetylcholine and NMDA receptors	Nausea and vomiting, dizziness, drowsiness, headache, ataxia, confusion and agitation, visual disturbances, constipation or diarrhoea, anorexia, mild transient generalised erythematous rash, leucopenia and other blood disorders	100-200	400-1200
Clobazam	$GABA_A$ receptor agonist	Drowsiness and light-headedness, confusion and ataxia, amnesia, dependence, aggression, muscle weakness	20-30	20-60
Gabapentin	Uncertain. Works on voltage-gated calcium channels	Diarrhoea, dry mouth, dyspepsia, nausea, vomiting, constipation, abdominal pain, flatulence, appetite changes, gingivitis, weight gain, hypertension, vasodilation, oedema, dyspnoea, cough, rhinitis, confusion, depression, hostility, sleep disturbances, headache, dizziness, anxiety, amnesia, ataxia, dysarthria, nystagmus, tremor, asthenia, paraesthesia, hyperkinesia, influenza-type symptoms, impotence, urinary incontinence, leucopenia, myalgia, arthralgia, diplopia, amblyopia, rash, purpura, pruritus, acne	300	900-3600

Lamotrigine	Blocks of voltage-dependent sodium channels	Rash (sometimes severe e.g. Stevens-Johnson syndrome or toxic epidermal necrolysis), hypersensitivity syndrome, nausea, vomiting, diarrhoea, hepatic dysfunction, headache, fatigue, dizziness, sleep disturbances, tremor, movement disorders, agitation, confusion, hallucinations, occasional increase in seizure frequency, blood disorders, arthralgia, lupus erythematosus-like effect, photosensitivity, nystagmus, diplopia, blurred vision, conjunctivitis, suicidal ideation	25	100-200
Levetiracetam	Unknown	Nausea, vomiting, dyspepsia, diarrhoea, abdominal pain, anorexia, weight changes, cough, drowsiness, asthenia, amnesia, ataxia, seizures, dizziness, headache, tremor, hyperkinesia, depression, emotional lability, insomnia, anxiety, impaired attention, aggression, irritability, thrombocytopaenia, myalgia, visual disturbances, pruritus, rash	250	250-1500
Oxcarbazepine	Blockage of sodium channels, affects potassium conductance and modulates high voltage-activated calcium channels	Nausea, vomiting, constipation, diarrhoea, abdominal pain, dizziness, headache, drowsiness, agitation, amnesia, asthenia, ataxia, confusion, impaired concentration, depression, tremor, hyponatraemia, acne, alopecia, rash, nystagmus, visual disorders including diplopia	600	600-2400
Pregabalin	Voltage-gated calcium channels	Dry mouth, constipation, nausea, vomiting, flatulence, oedema, dizziness, drowsiness, irritability, attention disturbance, disturbances in muscle control and movement, memory impairment, paraesthesia, euphoria, confusion, fatigue, appetite changes, weight gain, changes in sexual function, visual disturbances and ocular disorders	50	600

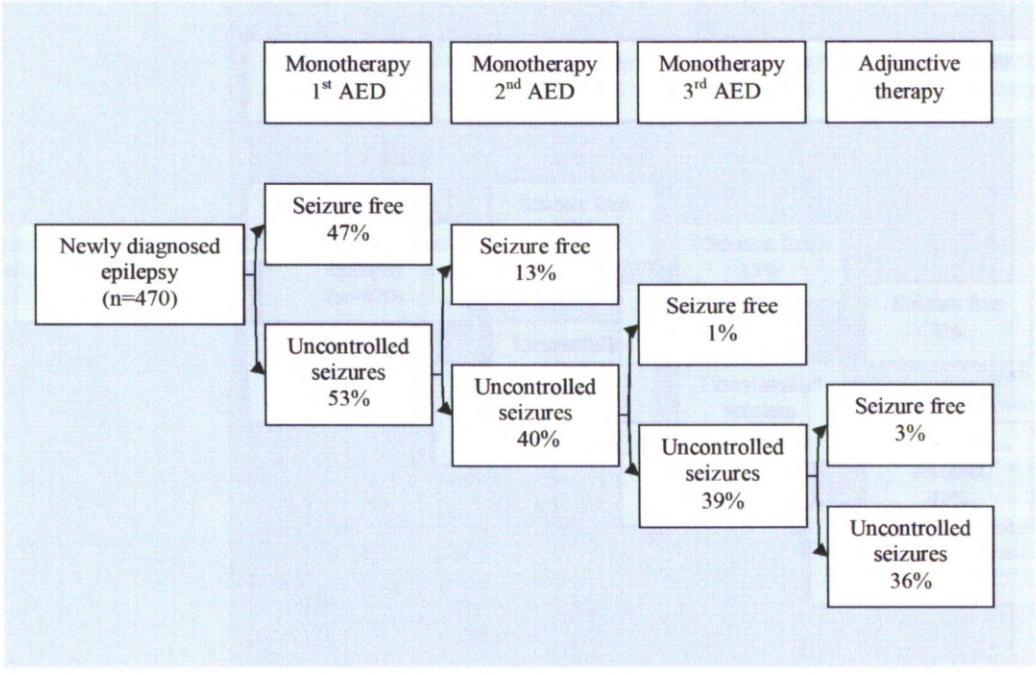
Topiramate	Blockage of sodium channels and calcium channels, enhances GABA neurotransmission, inhibits glutamate receptors, inhibit carbonic anhydrase	Nausea, abdominal pain, dyspepsia, diarrhoea, dry mouth, taste disturbance, weight loss, anorexia, paraesthesia, hypoaesthesia, headache, fatigue, dizziness, speech disorder, drowsiness, insomnia, impaired memory and concentration, anxiety, depression, visual disturbances	25	100
Valproate	Uncertain. Works on sodium channels and facilitates effects of GABA	Nausea, gastric irritation, diarrhoea, weight gain, hyperammonaemia, thrombocytopenia, transient hair loss (re-growth may be curly)	600	1000-2000

NMDA=N-methyl-D-aspartate, GABA=gamma-aminobutyric acid

2.3.2 Prognosis for people with epilepsy

For the majority of people, epilepsy is a relatively benign condition. Most people with newly diagnosed epilepsy will achieve seizure freedom. In the United Kingdom, the National General Practice Study of Epilepsy found that 54% of newly diagnosed patients were in five year remission, nine years after diagnosis (Cockerell *et al.*, 1995). However, approximately 20% of patients will never experience seizure remission. Better outcome is associated with absence of early life brain damage, absence of generalised epileptiform activity on EEG and no history of generalised tonic-clonic seizures (Shafer *et al.*, 1988).

Figure 2.4: The efficacy of AEDs in people with newly diagnosed (taken from Stein & Kanner, 2009 but data from Kwan & Brodie, 2000)



In terms of response to AEDs, a prospective long-term study of newly diagnosed patients in the UK showed that 64% of patients achieved at least a one year seizure remission after starting treatment (Kwan & Brodie, 2000). As shown in Figure 2.4, 47% became seizure free on the first drug; 13% on the second drug and 3% on the third drug. Only 1% became seizure

free on a combination of two drugs (Kwan & Brodie, 2000). This study also found that response to the first AED was the most powerful predictor of prognosis (Kwan & Brodie, 2000). Of those who become seizure free, approximately, 60-70% will be able to withdraw from AEDs without experiencing any further seizures (MRC Antiepileptic Drug Withdrawal Study Group, 1991, Kwan & Sander, 2004). Factors predicting outcome after withdrawal are length of seizure free periods, polytherapy, history of tonic-clonic or myoclonic seizures and seizures after the start of AED therapy (MRC Antiepileptic Drug Withdrawal Study Group, 1991). However, the decision to withdraw should be taken by the individuals, family and/or carers after full discussion of the risks and benefits by an epilepsy specialist (Stokes *et al.*, 2004).

Kwan and Sander (2004) have proposed that the prognosis of newly diagnosed epilepsy can be classified into three groups:

- **Excellent prognosis** characterises 20-30% of patients who will enter a long-term remission, probably even without AED treatment. If they are treated, they become seizure free on the first or second monotherapy, which can be withdrawn after a period of seizure freedom. This group may include those with benign neonatal seizures, benign rolandic epilepsy and childhood absence epilepsy.
- **Remission with treatment only** characterises 20-30% of patients who will remain seizure free only with continuing AED treatment. Some may require combination therapy and seizure may recur if treatment is withdrawn. This group may include those with juvenile myoclonic epilepsy and the majority of those with localisation-related epilepsies.
- **Continuing seizures despite treatment** characterises 30-40% of patients whose seizures recur despite AED treatment. This group may include those with symptomatic or cryptogenic localisation-related epilepsy, particularly, those associated with mesial temporal sclerosis, cortical dysplasia, structural brain lesions, progressive myoclonic epilepsies and West syndrome.

There are differing definitions as to what constitutes drug resistant or refractory epilepsy but a recent Task Force commissioned by the ILAE has recently defined it as '*as a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom*' (Kwan *et al.*, 2009).

Other treatment approaches

Epilepsy surgery

For those with drug resistant epilepsy, epilepsy surgery may be a potential option. The first surgical procedure to remove the epileptic focus in an individual with focal motor epilepsy was carried out by Horsley in 1886 (Daras *et al.*, 2008). Epilepsy surgery is a viable option for those who have an operable structural abnormality (e.g. hippocampal or medial temporal sclerosis). There are different types of resective surgical procedures which include: anterior temporal lobectomies; focal resections such as, amygdalohippocampectomy, where the hippocampus and amygdala are removed and lesionectomties where the structural lesion (e.g. cerebral tumour) is removed. There also different types of functional surgical procedures. These include corpus callostomy, hemispherectomy and multiple subpial transections. These are carried out to disrupt the pathways that are involved in the spread of epileptiform discharges, thereby reducing the frequency and severity of seizures. However, these do not remove the epileptogenic focus. A review of non-drug treatments for patients with drug resistant epilepsy found that approximately 55% of temporal lobe epilepsy patients were seizure free with no auras and 68% were seizure free with auras. After hemispherectomy, between 40-71.4% of patients were seizures free, although definitions of seizure freedom varied from study to study (Chapell *et al.*, 2003).

Vagal (vagus) nerve stimulation

For those who are not candidates for epilepsy surgery, vagal (vagus) nerve stimulation (VNS) may be used as an adjunctive therapy to pharmacological treatment in patients with partial seizures (with or without secondary generalisation) or generalised seizures that are refractory to antiepileptic medication. VNS is a non-pharmacological treatment whereby a small pulse

generator is implanted under the skin. This generates programmed pulses which stimulate the vagus nerve to reduce the frequency and severity of seizures. Around 43,000 people worldwide have been implanted with vagus nerve stimulators (Epilepsy Action, 2009). VNS is well tolerated and the adverse effects associated with implantation and stimulation are hoarseness, cough, dyspnoea, pain and paraesthesia. This is different from the side effects associated with antiepileptic drugs, suggesting that VNS is a good alternative for those individuals who have difficulty tolerating AEDs (Privitera *et al.*, 2002).

Ketogenic diet

Other treatment approaches include the ketogenic diet. This may be used as an adjunctive treatment in children with refractory epilepsy but should not be recommended for adults with epilepsy (Stokes *et al.*, 2004). The diet was first developed in the 1920s but has re-emerged as an effective treatment for those children who are drug resistant (Zupec-Kania & Spellman, 2008). It involves eating food that mimics the effects of starvation in the body i.e. a diet high in fat and low in carbohydrate and protein. This produces ketones but the mechanism underlying the effect on seizures is unclear. The diet needs input from a dietician and is restrictive. Eating at school or outside the home may be hard, which makes adherence to the diet difficult. The first randomised control trial published in 2008 found that after three months on the diet, 38% of children had more than a 50% reduction in seizures and 7% had more than a 90% reduction in seizures (Neal *et al.*, 2008). The adverse effects are, like VNS, different from the CNS side effects associated with AEDs. They include constipation, gastroesophageal reflux disease, kidney stones, abnormal lipid levels, growth retardation, hypoproteinaemia and micronutrient deficiencies (Zupec-Kania & Spellman, 2008).

Psychological intervention

Psychological intervention may include relaxation therapy, cognitive behavioural therapy, biofeedback and educational interventions. These should be used as adjunctive to pharmacological treatment rather than an alternative. However, a recent Cochrane review found no reliable evidence to support the use of psychological treatments in reducing seizure frequency and the authors recommended further trials (Ramaratnam *et al.*, 2008).

2.4 Summary

Epilepsy is a common neurological condition affecting approximately 50 million people worldwide. It is defined by the tendency to have recurrent epileptic seizures. It is a heterogeneous disorder characterised by different seizure types, syndromes and aetiologies. Antiepileptic drugs are the first approach in the management of seizures. The majority of people will respond to their first or second AED and will remain seizure free. However, for around 20-40% of people, their seizures will continue despite AED treatment and they may develop chronic, refractory epilepsy. Epilepsy surgery may be an alternative treatment option for some.

The ILAE has moved towards a definition of epilepsy that encompasses its neurobiological, cognitive, psychological and social consequences. For some people, these consequences can have a significant impact on their daily lives. For example, difficulties in areas of cognitive functioning can impact on academic achievement, occupational attainment, the ability to engage and maintain social relationships and overall quality of life. Therefore, in order to understand the effects of epilepsy on an individual, it is important to understand the factors that contribute to the development and maintenance of cognitive dysfunction in people with epilepsy. While some of these may be treatment-related, there are many other possible factors, as discussed in the next chapter.

Chapter 3 Neuropsychology of epilepsy

3.1 Overview of chapter

This chapter will review the literature on the neuropsychology of epilepsy. There will be a brief overview of the nature of cognitive impairments experienced by people with epilepsy, with evidence drawn from both objective and subjective reports. There will be a discussion of the causes of these impairments, which will include detailed considerations of the effects of epilepsy-related (e.g. epilepsy syndromes, aetiology and seizures), treatment-related (e.g. AEDs and epilepsy surgery) and psychosocial-related factors.

3.2 Cognitive functioning in people with epilepsy

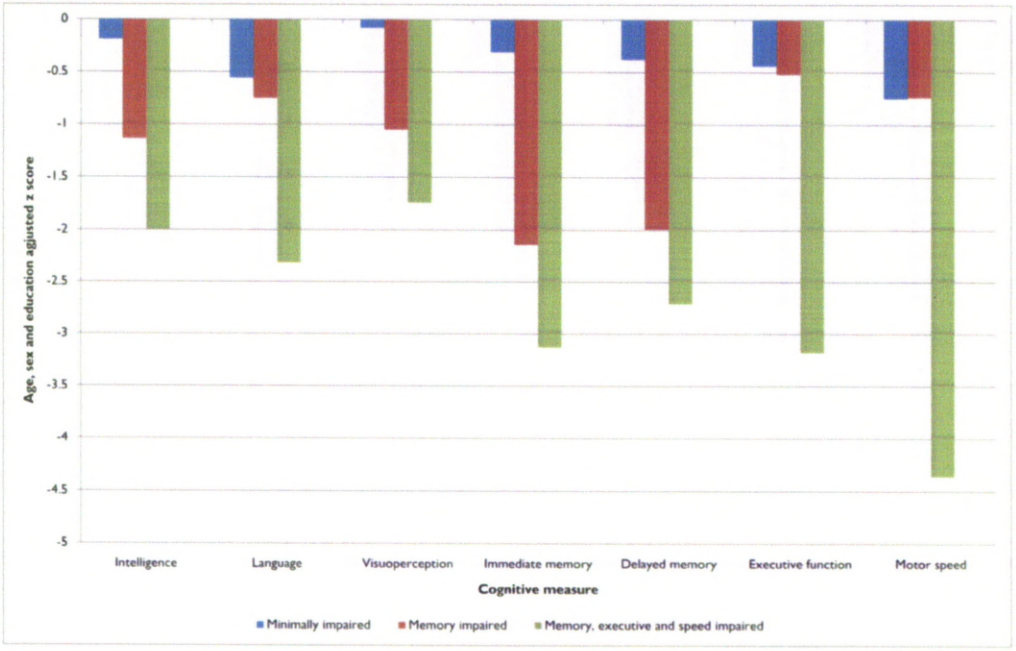
Since Ancient times, there has been recognition that epilepsy can have an adverse effect on cognitive functioning. The Greek physician, Aretaeus of Cappadocia (1st/2nd century BC), described how patients with chronic epilepsy tended to be '*languid, spiritless, stupid, inhuman and unsociable....slow to learn, from torpidity of the understanding and of the senses; dull of hearing...have utterances that are indistinct and bewildered, either from the nature of the disease, or from wounds during the attacks....*' (cited in Magiorkinis *et al.*, 2010). Aristotle described how people who have had epilepsy since childhood '*reach a mental state comparable to the stupor of extreme drunkenness*' (cited in Temkin, 1971). In the 19th century, Gowers (1885) commented that '*in its slighter forms there is merely defective memory, especially for recent acquisitions. In more severe degree there is greater imperfection of intellectual power, weakened capacity for attention and often defective moral control*' (cited in Temkin, 1971).

3.2.1 Performance on objective neuropsychological tests

With the advancement of the field of clinical neuropsychology in the 20th century, a number of studies have shown that people with epilepsy demonstrate impairments on objective neuropsychological tests. Several studies have shown that compared to people without

epilepsy, people with epilepsy have reduced memory and learning, attention and concentration problems, slowed information processing and psychomotor speed, language deficits and executive dysfunction (e.g. Hermann *et al.*, 1997, Baxendale *et al.*, 1998, Moore & Baker, 2002, Oyegbile *et al.*, 2004). However, there is considerable variation between people with epilepsy, which probably reflects the heterogeneity of the disorder. For example, Hermann *et al.*, (2007a) proposed three distinct cognitive profiles within people with chronic temporal lobe epilepsy: those who were minimally impaired (47%); those who were memory impaired (24%) and those who were memory, executive and speed impaired (29%).

Figure 3.1: The mean performance of three cognitive phenotypes in chronic temporal lobe epilepsy relative to healthy controls (represented by the x-axis) (data from Hermann et al., 2007a)



As shown in Figure 3.1, these different groups had a different pattern of neuropsychological performance across seven cognitive domains and a different pattern of performance compared with healthy controls. Those who were in the memory, executive and speed impaired group performed significantly worse compared to healthy controls and the other two groups across the measures. Those in this group were older, had a longer duration of

epilepsy and were taking more AEDs in comparison with the minimally impaired group. They also had more extensive neuroanatomic abnormalities, such as more abnormal cerebral volumes (e.g. white matter, grey matter and cerebrospinal fluid); more extensive cortical thinning and increased volume loss and atrophy in subcortical structures (e.g. the hippocampus and caudate), the corpus callosum and cerebellum (Hermann *et al.*, 2007a, Dabbs *et al.*, 2009). This suggests that some patients may be more susceptible to experiencing cognitive impairments and those who have a more severe course of epilepsy may be most at risk (Hermann *et al.*, 2007a).

3.2.2 Subjective report of cognitive problems

People with epilepsy are not only at risk of performing poorly on objective neuropsychological tests but they also frequently report experiencing subjective cognitive problems, which may affect their daily lives (e.g. Thompson & Corcoran, 1992, Baker *et al.*, 1997, Giovagnoli *et al.*, 1997, International Bureau for Epilepsy, 2004). A large European survey of more than 5000 people with epilepsy found that 50% of respondents reported experiencing memory problems; 48% had difficulty concentrating and 40% reported difficulties in thinking clearly (Baker *et al.*, 1997). A more recent European survey conducted by the International Bureau for Epilepsy (IBE) also found similar results. Fifty-nine per cent of the 425 respondents reported experiencing sleepiness or tiredness; 48% lethargy or sluggishness; 45% slowness of thought and 44% reported difficulties in learning something new. A significant proportion of respondents felt that these cognitive effects had a noticeable impact on their work (50%), family and relationships (50%), leisure pursuits (46%) and education (45%) (IBE, 2004). Thompson & Corcoran (1992) explored the type of everyday memory failures that people with epilepsy commonly experience. They found the most frequent problems were: 'tip of the tongue' phenomena (reported by 43%); going back to check whether something has been done (39%) and forgetting where things have been put (33%). Fifty-four percent of respondents regarded these memory failures as a moderate or serious nuisance on their day to day lives.

Cognitive problems are not only reported by adults with epilepsy. In another recent survey by the IBE on the impact of epilepsy and its treatment in children with epilepsy, children

commonly reported experiencing difficulties working out sums; solving problems; concentrating; describing things to other people and remembering things. Many children reported feeling worried about being able to keep up with their schoolwork. More than a third felt that epilepsy would impact on their lives in the future, affecting their employment opportunities and continuing education (Baker *et al.*, 2008).

3.2.3 Discrepancy between objective and subjective report

Despite studies that provide evidence of both objective and subjective reductions in cognitive performance, there are also several studies that have suggested that there is a lack of correlation between subjective reports of cognitive complaints and performance on objective neuropsychological tests (e.g. Thompson & Corcoran, 1992, Elixhauser *et al.*, 1999, Piazzini *et al.*, 2001, Andelman *et al.*, 2004, Liik *et al.*, 2009, Marino *et al.*, 2009). Several studies have suggested that some patients tend to overestimate their problems, while others have suggested that some tend to underestimate them. There have been several reasons proposed to explain the discrepancy between objective and subjective report (see Table 3.1).

Table 3.1: Explanations for discrepancy between objective and subjective report

Anxiety and depression	• May lower self-esteem, causing patients to over-report their difficulties (Thompson & Corcoran, 1992, Corcoran & Thompson, 1993, Giovagnoli *et al.*, 1997, Piazzini *et al.*, 2001, Liik *et al.*, 2009, Marino *et al.*, 2009, Salas-Puig *et al.*, 2009)
Personality traits (e.g. neuroticism)	• Have been associated with an increased number of cognitive complaints (Vermeulen *et al.*, 1993, Uijl *et al.*, 2006)
Right hemisphere epileptogenic lesions	• Have been associated with a systematic bias in self-awareness for memory, which may cause a tendency to over-estimate memory abilities (Andelman *et al.*, 2004)
Neuropsychological tests may not measure everyday difficulties	• E.g. remembering names of familiar people, remembering where things have been put, or remembering personal facts or events (remote memory) is different from remembering a list of unrelated words in a verbal list learning task (Elixhauser *et al.*, 1999)
Patient's concepts of memory problems are different from those of a neuropsychologist	• E.g. patients may consider forgetting the names of objects a memory problem but a neuropsychologist would consider this a naming deficit and would assess this using a confrontation naming task (Helmstaedter & Elger, 2000)
Impairment of long-term recall beyond what is assessed in traditional memory assessments	• Patients may demonstrate 'normal' learning and memory over these relatively short retention intervals but have accelerated forgetting over longer intervals (e.g. days and weeks) (O'Connor *et al.*, 1997, Blake *et al.*, 2000, Mameniskiene *et al.*, 2006)

The discrepancy between subjective and objective report means that clinicians and researchers need to be aware that patient's perceptions of their cognitive problems (or lack of problems) may not accurately reflect their cognitive abilities, as measured on objective tests. A reliable and comprehensive neuropsychological assessment, taking into account emotional state and the nature of self-reported difficulties, may be needed to uncover the extent of cognitive dysfunction in an individual patient (Thompson & Corcoran, 1992, Piazzini *et al.*, 2001).

3.3 Causes of cognitive impairment in people with epilepsy

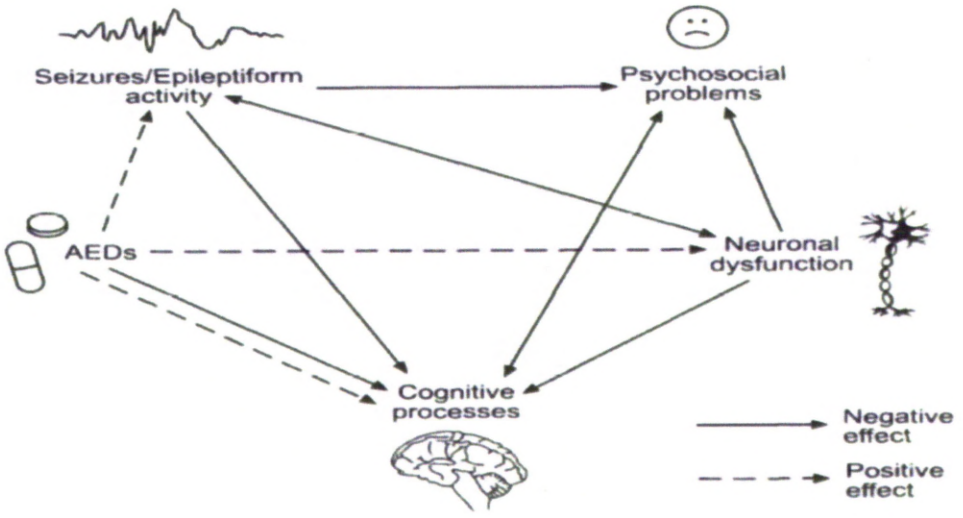
Despite these discrepancies, it is clear that people with epilepsy are at risk of developing cognitive impairment. As cognitive impairment can have a negative impact on day to day functioning (e.g. education, employment, family life and social relationships), psychological well-being (e.g. self-confidence, self-esteem, anxiety and depression) and overall quality of life (Perrine & Kiolbasa, 1999, Giovagnoli & Avanzini, 2000, Baker *et al.*, 2009, Meneses *et al.*, 2009), it is important to understand the factors that contribute to the maintenance and development of cognitive dysfunction. There are several factors, as shown in Table 3.2. These include: the effects of the underlying aetiology, the effects of recurrent seizures; the side effects of antiepileptic drug treatment and psychosocial issues (Kwan & Brodie, 2001, Meador, 2002, Motamedi & Meador, 2003, Aldenkamp & Bodde, 2005).

Table 3.2: Factors affecting cognitive functioning in people with epilepsy

Aetiology	• Presence of underlying brain damage • Localisation of epileptogenic focus
Epilepsy-related factors	• Epilepsy syndrome • Age of onset
Seizure-related factors	• Seizure type • Seizure frequency • Duration of epilepsy • Interictal activity • Status epilepticus
Treatment-related factors	• Type of AED • Dose • Drug interactions • Epilepsy surgery • Vagal nerve stimulation
Psychosocial-related factors	• Depression and anxiety • Public attitudes/stigma • Self-esteem • Educational/occupational attainment

There are complex potential interactions between these factors, as shown in Figure 3.2. Antiepileptic drugs, for example, can both enhance, by improving seizure control, and impair cognition, whereas seizure activity, psychosocial problems and neuronal dysfunction may have a negative effect (Aldenkamp, 2006). These complex interactions make it difficult to determine their individual relative contribution to cognitive dysfunction. However, there has been a significant body of research undertaken to understand the causes of cognitive impairments, in particular the cognitive side effects of antiepileptic drug treatment. In the following sections, there will be a review of the literature investigating the cognitive effects of each of these epilepsy, treatment and psychosocial-related factors.

Figure 3.2: Non-independent contributory factors for cognitive dysfunction (Aldenkamp, 2006)



3.3.1 Epilepsy-related

Epilepsy syndrome and underlying aetiology

Symptomatic/cryptogenic epilepsies

As defined in the previous chapter, symptomatic epilepsy is the result of a lesion or other underlying identifiable pathology, and cryptogenic epilepsy is when the cause is unknown but is presumed to be symptomatic. Some of these underlying aetiologies can impact on cognition independently of epilepsy-related factors, such as seizures or antiepileptic drug treatment (Elger *et al.*, 2004)[3]. Table 3.3 highlights some of the neuropsychological problems associated with both developmental and acquired lesions such as cortical dysplasia, cerebral tumour and ischemic infarction. There are also independent effects on cognition of CNS infection,

[3] As discussed in the next chapter, there is a growing body of evidence suggesting that people with newly diagnosed epilepsy are already cognitively compromised at the time of diagnosis, implicating a strong role for the underlying aetiology. However, other factors (e.g. epileptogenesis and psychological factors) may be contributing to the observed cognitive dysfunction, further illustrating the complexity of untangling the causes of cognitive impairment in people with epilepsy

traumatic brain injury and degenerative CNS disease (Jokeit & Schacher, 2004). These different pathologies can give rise to different cognitive consequences of varying severity (Kwan & Brodie, 2001).

In symptomatic epilepsy the pattern of cognitive deficits are often consistent with the localisation of the lesion. For example, lesions in the language-dominant hemisphere may result in verbal deficits or lesions in the frontal lobes may result in executive dysfunction. One of the most studied findings is the effects of temporal lobe epilepsy, particularly mesial temporal lobe epilepsy (MTLE), on memory functioning. The medial temporal lobes have been heavily implicated in memory processes and the hippocampus seems necessary for establishing long-term declarative memory (e.g. Scoville & Milner, 1957, Milner *et al.*, 1968). Therefore, it is unsurprising that patients with MTLE usually present with memory deficits (Glowinski, 1973, Hermann *et al.*, 1997, Baxendale *et al.*, 1998, Oddo *et al.*, 2003). In addition to the effects of MTLE, there is also lateralisation of memory functioning producing material-specific memory deficits. Left temporal lobe epilepsy (TLE) is more commonly associated with verbal memory deficits, whereas right TLE is more typically associated with non-verbal memory deficits, although this association is less consistently reported (Elger *et al.*, 2004).

Table 3.3: Neuropsychological deficits associated with lesion-related epilepsy (adapted from Morrison & Nakhutina, 2007)

Developmental lesions	Malformations of cortical development	Tuberous sclerosis complex	• Large proportion of patients have learning disabilities and severe cognitive dysfunction • Some patients have IQ in normal range but deficits noted in attention, memory and executive functioning • Cognitive deficits largely reflect location of abnormalities
		Focal cortical dysplasia	• High proportion of patients have learning disabilities and developmental delay and rate is higher in those with extratemporal lobe lesions • Severity of epilepsy syndrome is related to degree of cognitive delay • Younger age of seizure onset and size of lesion is associated with greater cognitive impairment
		Focal heterotopias	• Can be associated with developmental delay, mild cognitive impairment and learning disabilities but many patients will have normal cognition
		Hypothalamic hamartomas	• Better cognitive functioning if seizures start in adulthood rather than in childhood • Cognitive performance related to the size and volume of the lesion
		Polymicrogyria	• Many different types of polymicrogyria so cognitive functioning is variable • Cognitive functioning is related to the size of the malformation
		Schizencephaly	• Variable pathology so no typical cognitive profile • Cognitive dysfunction can vary from mild to severe • More focal lesions associated with normal cognition
	Vascular malformations	Arteriovenous malformations (AVM)	• Cognitive deficits present in 60-80% of cases • Deficits reported in verbal and visual memory, attention, language and visuoconstructional abilities, perceptual and organisational skills, fluency, rapid set-shifting, motor speed and finger dexterity but debate as to whether general intellectual functioning is affected • No clear relationship between size and site of AVM suggesting adaption and reorganisation of cortical functions
		Cavernous malformations	• Information on cognitive deficits come mainly from case studies • Deficits are usually focal e.g. executive dysfunction in patient with cavernous malformations in anterior cingulate cortex

Foreign tissue lesions	Intracranial tumours	Intracranial tumours	• One study found that 90% of patients with temporal or frontal tumours had cognitive impairments in at least one area (Tucha *et al.*, 2000). • Attention, memory and executive functioning are domains most commonly affected. • Cognitive deficits relate to type of lesion, location, size, rate of growth, oedema, increased intracranial pressure, ischemia, hypoxia, haemorrhage, necrosis, obstructive hydrocephalus and changes in neurotransmitters • Cognitive problems may be more apparent in those with low grade tumours and slow-growing lesions may not produce as many severe deficits
	Cysts	Arachnoid cysts	• Associated with impaired processing speed, memory, visual attention, visuoconstructional skills and executive functioning
		Porencephalic cysts	• Relatively normal functioning has been reported in some individuals where porencephalic cysts develop early in life but have also been associated with significant cognitive delay
Acquired lesions	Stoke, infarction, haemorrhage	Ischemic infarctions	• Cognitive deficits are lateralised to the side of lesion. Nature of deficits depends on size and site of infarction
		Haemorrhagic stroke	• Fewer cognitive deficits, if bleeding is stopped quickly. More widespread deficits seen if damage is more extensive • Variation in nature and severity of cognitive deficits • Subarachnoid haemorrhage can cause generalised deficits due to initial bleed and subsequent complications. Deficits been reported in verbal and visual memory, psychomotor speed, visuospatial functioning, executive functioning, attention, cognitive speed and flexibility

However, some have suggested that people with temporal lobe epilepsy, not only have memory impairments, but have a more generalised pattern of cognitive impairment, involving functions associated with other regions, for example, executive dysfunction (Hermann *et al.*, 1988, Corcoran & Upton, 1993, Hermann *et al.*, 1997, Oyegbile *et al.*, 2004). This suggests that the spread of epileptic activity along neural connections between cortical regions (e.g. temporal lobe and prefrontal cortex) may be causing effects in areas distant from the region initially affected (Hermann *et al.*, 1997). Alternatively, they may be the result of more diffuse generalised abnormalities throughout the brain (Hermann *et al.*, 2009). In support of this, several quantitative MRI studies have shown atrophy of both temporal and extratemporal regions in those with chronic temporal lobe epilepsy (e.g. Hermann *et al.*, 2007a, Keller & Roberts, 2008, Dabbs *et al.*, 2009, Keller *et al.*, 2009). However, others have suggested that a deficient hippocampus may be causing impairments, particularly on traditional frontal lobe tasks, such as the Wisconsin Card Sorting Test (Corcoran & Upton, 1993, Upton & Corcoran, 1995, Giovagnoli, 2001). Additionally, other factors such as medication, seizures and mood may be contributing to the pattern of generalised impairment.

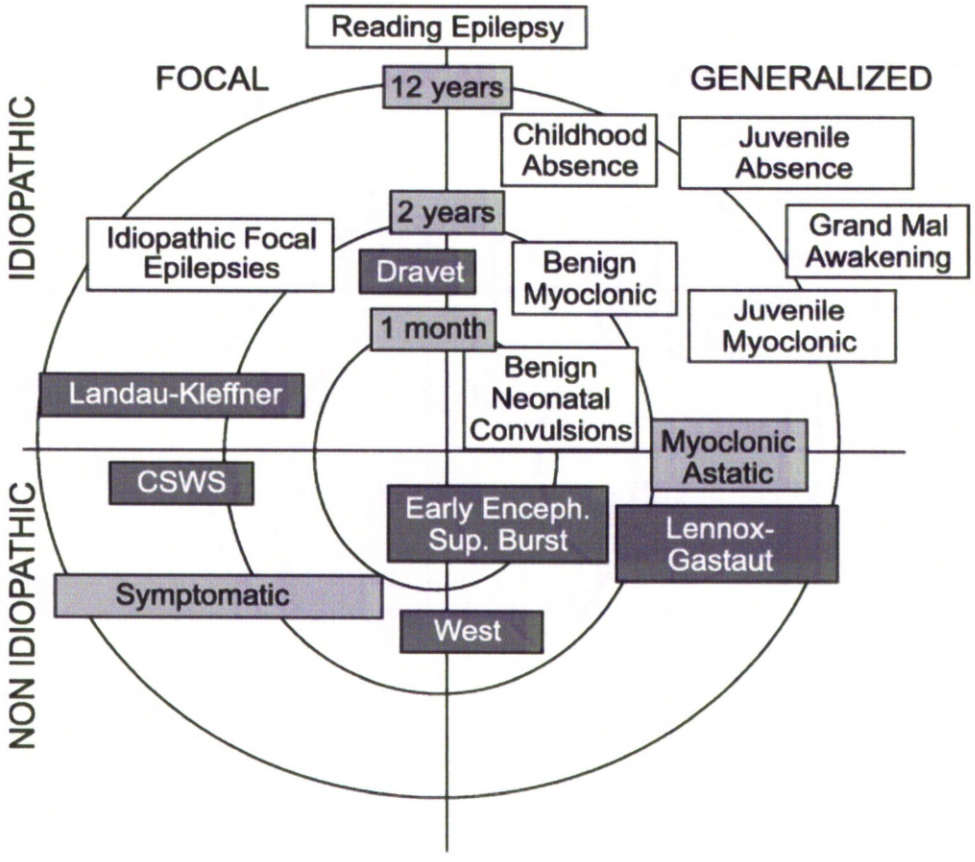
Idiopathic epilepsies

Those with idiopathic epilepsy are more likely to have normal intelligence than those who have symptomatic epilepsy (Klove & Matthews, 1966, Meador, 2002). However, despite normal intellectual functioning, there is still evidence of mild cognitive impairment in other domains (Klove & Matthews, 1966). For example, several studies have shown a neuropsychological profile of executive function deficits, along with impaired verbal and visual memory, in those with juvenile myoclonic epilepsy (e.g. Sonmez *et al.*, 2004, Hommet *et al.*, 2006, Pascalicchio *et al.*, 2007, Piazzini *et al.*, 2008, Iqbal *et al.*, 2009). Elger *et al.*, (2004) noted that the idiopathic epilepsies make good models for studying the effects of epilepsy on cognition because they do not have the confounding effects of additional cerebral disease, and seizures are usually well-controlled, which removes the negative effects of recurrent seizures. However, because many people with idiopathic epilepsy do not experience cognitive deficits, there are relatively few studies on their neuropsychological outcome.

Epileptic encephalopathies

Some specific epilepsy syndromes have been associated with severe cognitive impairment (Hirsch *et al.*, 2003). As shown in Figure 3.3, some of the childhood epilepsy syndromes are associated with severe cognitive dysfunction, such as West syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome and epilepsy with continuous spike-waves during sleep. These syndromes are known as epileptic encephalopathies, which are conditions in which the cognitive dysfunction is mainly due to epileptic activity [either very frequent or severe seizures and/or severely abnormal interictal EEGs (Holmes & Lenck-Santini, 2006)]. In these syndromes, once seizures are stopped, with either medications or surgery, children can regain normal cognitive function (Holmes & Lenck-Santini, 2006).

Figure 3.3: Epilepsy syndromes and cognitive deficits (taken from Hirsch et al., 2003)



Age of onset

A separate but related factor is age of onset of epilepsy. Age of onset may modify the effects of epilepsy on cognitive functioning and has been shown to be a significant predictor of cognitive outcome in people with epilepsy (e.g. Schoenfeld *et al.*, 1999, Aikia *et al.*, 2001, van Mil *et al.*, 2008). Several studies have suggested that younger age of onset is associated with more cognitive problems (e.g. Meador, 2002, van Mil *et al.*, 2008). An early study by Dikmen *et al.,* (1975) compared those who had a seizure onset under the age of five with those who had a later age of onset between 10-25 years. Those who had an early age of onset performed more poorly on the neuropsychological test battery than those in the later age of onset group and this was significantly lower for measures of intellectual functioning, even after controlling for seizure duration and seizure frequency. Similarly, O'Leary *et al.,* (1983) found that those whose seizures began before the age of five years performed significantly worse than those whose seizures began after the age of five, also after controlling for duration of epilepsy.

An earlier age of onset may be associated with cognitive dysfunction due to the impact of epilepsy on a developing brain. Early disruption to normal developmental processes (e.g. synaptogenesis and myelination) can have severe consequences for ongoing cognitive development (Anderson *et al.*, 2001, Brown, 2006). Also, an early age of onset may reflect greater seizure-induced damage, due to the increased risk of a higher number of lifetime seizures and longer treatment with AEDs. As discussed below, these all have an additional impact on cognition. However, a greater impact with earlier age of onset does not fit with previous research that has suggested a greater potential for recovery of function in children due to the plasticity of the developing brain, which can lead to compensation or cerebral and functional reorganisation (e.g. Muller *et al.*, 1998).

Effects of seizures

Immediate impact of seizures

During a seizure, cognitive impairments (e.g. confusion, aphasia) may occur as part of the clinical manifestation. In addition, seizures may directly affect alertness, short-term learning

and problem solving. Nocturnal seizures may affect language functions, memory and alertness possibly through the effects of disturbed sleep (Aldenkamp, 1997). Postictally, cognitive functioning, particularly attention, may still be affected, although this may not be prolonged (Aldenkamp & Bodde, 2005). Goldberg-Stern *et al.,* (2004) assessed postictal language effects in those with frontal-onset complex partial seizures. Seizures confined to the non-dominant frontal lobe had the shortest postictal language delay (mean 17.3 seconds) whilst those originating in the dominant frontal lobe but spread to the ipsilateral temporal lobe had the longest delay (median 546.8 seconds). Dodrill (1986) suggested that performance on neuropsychological tests may be impaired for up to 30 days after a seizure. Therefore, postictal effects should be borne in mind, especially when assessing a patient, particularly for epilepsy surgery. However, subsequently, Dodrill & Ojemann (2007) carefully monitored patients to make sure that they were neither immediately ictal nor postictal and found no cognitive impact of seizures that had occurred on, or the day before, neuropsychological testing. The authors suggest that with careful evaluation, recent seizures should not have effects on neuropsychological test performance.

Effects of epileptiform EEG discharges

Whilst there is debate about whether recent seizures affect cognitive testing, interictal epileptiform EEG discharges, which are not accompanied by obvious clinical manifestations (subclinical), may cause transitory cognitive impairment (TCI). This impairment is different from that caused by the ictal/postictal effects of seizures, discussed above. TCI has been defined as '*an episode of cognitive impairment occurring exclusively during an episode with epileptiform discharges and without any other clinical signs*' (Aldenkamp & Arends, 2004). This means that the cognitive impairment cannot be the result of subtle or brief minor seizures (Aldenkamp & Arends, 2004). As a result, 'genuine' TCI can be difficult to diagnose and is considered to be a controversial concept (Aldenkamp & Arends, 2004). This is because some have argued that if a discharge is causing an alteration in cognition, then this fits into the definition of an epileptic seizure (Aarts *et al.*, 1984, Binnie *et al.*, 1987, Binnie, 2001).

TCI can be detected using sensitive neuropsychological tasks in combination with EEG and video monitoring (Binnie *et al.,* 1987). The most sensitive tasks are those that are more

difficult and measure higher cortical functions such as choice reaction time, signal detection, short-term memory and information processing. Simple motor tasks or those that do not require complex information processing seem to be little affected by epileptiform EEG discharges (Aldenkamp & Arends, 2004). The most commonly used tasks are often presented as computer games (Binnie, 2001), for example, two short-term memory computer game tasks developed by Aarts *et al.,* (1984). Using these tasks, Aarts *et al.*, (1984) found: i) TCI in 50% of patients with interictal epileptiform discharges; ii) cognition was most affected when discharges occurred during stimulus presentation, and iii) evidence for laterality effects. Left-sided discharges caused impairments on the verbal version (verbal working memory task) and right-sided discharges caused impairments on the spatial version (non-verbal working memory task). This finding was replicated in a larger series of patients using the same assessment materials (Binnie *et al.,* 1987).

TCI may affect educational and occupational functioning (Aarts *et al.,* 1984). It has been shown to impact on daily living skills (e.g. driving, reading), avoiding everyday hazards (e.g. crossing the road), and social interaction (e.g. missing parts of conversations, failure to respond at the appropriate moment) (Kasteleijn-Nolst Trenite *et al.*, 1987, 1988, Marston *et al.*, 1993). Suppressing these subclinical epileptiform discharges, through AED medication, may improve psychosocial function, as illustrated in two case studies by Aarts *et al.*, (1984) and a randomised double-blind, cross-over trial undertaken in children with epilepsy (Marston *et al.,* 1993).

Transient epileptic amnesia

Transient epileptic amnesia (TEA) may also have an immediate impact on cognitive functioning, specifically, memory functioning. TEA is a recently described syndrome, and is a form of temporal lobe epilepsy, where *'the principle manifestation of seizures is episodes of transient amnesia during which other functions remain intact'* (Butler *et al.*, 2007, Butler & Zeman, 2008). Butler & Zeman (2008) have recently published a review of all case reports and case series of TEA associated with epilepsy. They found 94 cases in the literature. Table 3.4 summarises the demographic and clinical characteristics of the cases.

Table 3.4: Clinical characteristics of the syndrome of transient epileptic amnesia

Transient epileptic amnesia
• Syndrome of middle to old age • More common in males than females (sex ratio two males to one female) • Median duration of amnesic attacks of 30-60 minutes, which is longer than typical temporal lobe seizures but shorter than transient global amnesia (a similar syndrome which results in transient impairment of declarative memory due to neuronal dysfunction in the temporal lobes) • Mean frequency of attacks of 14.8 per year but wide variability between individuals • Association between an amnesic attack and arousal from sleep in 70.4% of cases • Characterised by anterograde and/or retrograde amnesia • May sometimes be accompanied by other features e.g. olfactory/gustatory hallucinations, déjà vu and automatisms (all of which are commonly associated with temporal lobe epilepsy) • Interictal memory dysfunction reported in 80.6% of patients but the majority performed normally on standard neuropsychological tests. Accelerated long-term forgetting and remote autobiographical memory loss may explain this discrepancy (Butler *et al.*, 2007)

Although the mechanisms underlying the syndrome are still unclear, TEA may be due to non-convulsive status epilepticus or may be a result of postictal amnesia possibly following subclinical/interictal epileptiform discharges (Butler & Zeman, 2008).

Effects of seizure type

Some studies have suggested that generalised tonic-clonic seizures (GTCS) are associated with a greater risk of cognitive impairment than partial seizures (Aldenkamp & Bodde, 2005). However, other studies have found inconsistent findings. O'Leary *et al.*, (1983) demonstrated that the performance of 106 children with partial seizures was similar to that of children with generalised seizures. There was only one significant difference between the two groups across a neuropsychological test battery; children with partial seizures performed better than those with generalised seizures on the memory subscale of the Tactual Performance Test (a measure of incidental memory for shapes). Similarly, there were no differences between those with partial or generalised seizures in a study of 52 newly diagnosed adult patients with epilepsy (Pulliainen *et al.*, 2000a).

Equally, others have found no differences between those with simple, complex and secondarily generalised seizures, for example, the study by O'Leary *et al.*, (1983); although, they did find a difference on one measure, with those with secondarily GTCS performing more poorly on the location subscale of the Tactual Performance Test (a measure of incidental

memory for spatial location). However, Prevey *et al.,* (1998) found that newly diagnosed patients with complex partial seizures tended to perform better than those with secondarily generalised seizures on most cognitive measures, particularly, those that required concentration and mental flexibility. The presence of secondarily generalised seizures has also been identified as a risk factor for moderate impairment of verbal memory in patients with newly diagnosed left temporal lobe epilepsy (Aikia *et al.,* 2001). Prevey *et al.,* (1998) suggested that this may be the result of more extensive neural abnormality and structural damage in those with secondarily generalised seizures or may result from the different pathophysiology of the two types of seizures. As generalised seizures involve loss of consciousness due to disruption of the central arousal systems, this may lead to hypoxic-metabolic damage or cell death from excitotoxic effects. Also, disruption to these central arousal systems impacts on attention and concentration, which may then contribute to poorer performance on other cognitive tasks (Mirsky *et al.*, 1960, Prevey *et al.*, 1998).

Effects of seizure frequency

More frequent seizures have been associated with greater risk of cognitive impairment (Meador, 2002). An early study by Blakemore *et al.,* (1966) investigated the relationship between frequency of seizures and severity of neuropathology and intellectual functioning. They grouped patients into four groups on the basis of their frequency of seizures (more/less than three per week) and severity of neuropathology (minimum/maximum based on a pathological grading scale). There were no differences between the four groups, but while not statistically significant, those with higher frequency of seizures (more than three per week) had poorer intellectual functioning. Similarly, Dikmen & Matthews (1977) divided 72 patients with 'major motor' (generalised tonic-clonic) seizures into low, moderate or high seizure frequency groups. There were significant differences between the three groups on seven of the cognitive measures. Those with high seizure frequency performed more poorly than those with low seizure frequency. The moderate seizure frequency group were in the middle, as expected, for 13 of the 14 measures. Some of the differences could be considered clinically significant, for example, the mean raw IQ scores for the high seizure frequency group were more than one standard deviation (SD) lower than the low seizure frequency group [Full Scale IQ (FSIQ) 81.04 vs. 94.96]. Impairments were more pronounced in those who also had a long

seizure history and early age of onset. Those with more frequent seizures often have higher AED dosages; are on polytherapy; are at increased risk of psychosocial issues and have a more severe underlying pathology, which may also be impacting on cognition, in addition to the direct effects of seizures.

Accumulating impact of recurrent seizures

The association between higher seizure frequency and cognitive impairment may be due to a more severe underlying brain disorder that is leading to recurrent seizures or recurrent seizures may be damaging the brain. There is a long-standing, continuing debate about whether seizures cause brain damage (e.g. review by Sutula & Pitkanen, 2002). A series of animal studies have suggested that repeated seizures cause molecular and genomic alterations, such as protein expression, synaptic reorganisation, necrosis and apoptosis, which cause long-term structural and functional changes (e.g. Cole *et al.*, 2002). In humans, the results are less conclusive. A series of imaging studies have found progressive loss of volumes with longer duration of epilepsy (Briellmann *et al.*, 2002, Fuerst *et al.*, 2003, Liu *et al.*, 2003). However, whilst this may reflect secondary cerebral damage from seizures, it may also be the result of the underlying epileptic process (Duncan & Thompson, 2003). Consistent with this, an increased risk of neocortical damage identified in the longitudinal study by Liu *et al.*, (2003) was not related to a history of documented convulsive or partial seizures but the authors speculated was possibly related to an underlying epileptic process or longer exposure to AEDs or an increased genetic susceptibility to brain insults.

Other evidence that supports the idea of an accumulating impact of recurrent seizures comes from studies that have found a relationship between lifetime number of seizures and cognitive dysfunction. Increasing number of seizures were related to poorer intellectual functioning and poorer performance across a neuropsychological test battery in a study by Dodrill (1986). Those that had a history of more than 100 GTCS had the most declines in functioning and greater maladjustment and emotional problems. Similarly, Vlooswijk *et al.*, (2008) investigated the effects of secondarily generalised seizures on cognitive functioning in 16 patients with localisation-related epilepsy using both neuropsychological assessment and fMRI (functional Magnetic Resonance Imaging). Those with a higher number of secondarily GTCS had lower

IQ scores, and a trend towards more global cognitive deterioration, than those with a lower number of secondarily GTCS. In addition, a higher number of secondarily GTCS was associated with an increase in prefrontal activation and a trend towards decreased temporofrontal activation. The authors suggest that increased exposure to seizures led to a functional reorganisation of working memory. However, it is unclear whether this reflects a compensation strategy or the underlying pathological process of cognitive dysfunction.

Additionally, duration of epilepsy is a marker for lifetime number of seizures and several studies have found a relationship between duration of epilepsy and cognitive decline[4]. Cognitive decline has been significantly associated with frequency of seizures (Upton & Thompson, 1997, Helmstaedter *et al.*, 2003, Thompson & Duncan, 2005, Piazzini *et al.*, 2006) and improvements in seizure frequency have been associated with cognitive improvements (Rodin, 1968, Seidenberg *et al.*, 1981). Seizures may not just impact on the site of the epileptogenic focus but may have more widespread effects. Blum (2001) carried out a cross-sectional study in 30 patients with right TLE and medial temporal sclerosis who were undergoing presurgical evaluation. Using the intracarotid amobarbital (Wada) test, they assessed verbal memory functioning in the contralateral temporal lobe. Verbal memory functioning was significantly negatively associated with longer duration of epilepsy and increased lifetime number of seizures, suggesting that seizures in the right temporal lobe led to progressive dysfunction of memory in the contralateral side.

However, there are many methodological difficulties with studies trying to isolate the specific cognitive effects of seizures. As noted in a review by Vingerhoets (2006), it is difficult to untangle the long term effects of epilepsy from the underlying lesion. Many studies fail to document the type and number of seizures, and many cannot separate out the highly inter-related variables of duration of epilepsy, interictal brain activity, number of seizures, exposure to AEDs, age of onset and number of seizure-related head injuries. This led to a conclusion that '*there is a mild but measurable decline of intellectual performance...In adults, memory*

[4] The issue of progressive decline with increasing duration of epilepsy will be discussed in the next chapter, although this will not discuss the specific effects of seizures on cognitive decline but will review the evidence from the literature investigating cognitive change over time.

appears to be the most vulnerable cognitive function. Due to many confounding effects, the effects of seizures per se is difficult to estimate, but appears limited'.

Status epilepticus

Status epilepticus (convulsive and non-convulsive) can also contribute to cognitive deterioration (Dodrill & Wilensky, 1990, Helmstaedter, 2007). Dodrill & Wilensky (1990) reviewed the early literature on cognitive outcome after SE. They highlighted several methodological problems with previous work, such as lack of formal neuropsychological assessment and that the majority of studies were retrospective. However, they concluded that '*there are undoubtedly some adverse effects, at least under certain circumstances, but the circumstances under which such effects appear and the degree and nature of further effects require further study*'. They also reported results of their prospective longitudinal study. They followed-up 143 adults with epilepsy over a five year period. Of those, nine patients had at least one definitive episode of status during the interval. Four had experienced generalised tonic-clonic status and five had experienced complex partial SE. They were then matched on sex, age and education with nine patients who did not experience status. However, interestingly, across the neuropsychological test battery, the status group demonstrated mild to moderate impairment at baseline, with 72% of test variables falling outside normal limits compared with 46% for the non-status group. Additionally, the status group had a Full Scale IQ score that was a mean 14 points lower than the non-status group (Mean FSIQ 99.78 vs. 85.56). The authors suggested that this implies that those who are more compromised in functioning are more likely to experience SE. After five years, the non-status group improved across the battery due to practice effects [e.g. Mean Performance IQ (PIQ) 99.89 at baseline vs. 107.80 after five years; % of tests outside normal limits significantly decreased from 46% to 31%]. However, the status group either did not improve or declined in functioning [e.g. Mean Verbal IQ (VIQ) 90.44 at baseline vs. 85.89 after five years]. Not all of these differences reached statistical significance, probably due to the small sample size. The authors concluded that SE has a slight adverse effect on cognitive abilities, which may represent a lack of practice effect rather than abject decline, but this may be greater for some individuals.

A more recent review of cognitive outcomes after SE by Helmstaedter (2007) suggests that outcomes vary with age, the type and aetiology of epilepsy and the severity of status. The review also found evidence to support the view that pre-existing brain damage and cognitive impairments may lead to an increased risk of experiencing status rather than status causing the impairments.

Summary of the effects of seizures

Seizures are brief episodes of abnormal brain activity. Yet these brief episodes can produce cognitive effects that may be more debilitating than the seizure themselves. These effects can persist beyond the seizure and there is growing evidence that recurrent seizures can cause significant damage to the brain, potentially leading to a decline in cognitive functioning. Therefore, it is important that people with epilepsy achieve optimum seizure control and if seizures are refractory to medical treatment then early referral for epilepsy surgery could potentially stop further damage.

3.3.2 Treatment-related factors

Antiepileptic drug treatment

Patient perceived effects on cognition

Adverse effects of antiepileptic drugs are frequently reported, occurring in approximately 60%-70% of patients (Perucca & Meador, 2005, Carpay *et al.*, 2005, Uijl *et al.*, 2006). CNS side effects are particularly common and include symptoms such as fatigue, headache, blurred vision, dizziness, as well as cognitive impairments. A community-based population survey in The Netherlands, found that 62% of respondents reported experiencing cognitive side effects, of which memory problems were the most frequent (21.4%) (Carpay *et al.*, 2005). Sixty-one per cent of respondents in the IBE Cognitive Function survey (2004) had asked a healthcare professional whether their cognitive side effects could be reduced or improved. Additionally, a US survey found that 30-40% of respondents felt that their medication had a large negative impact on their cognitive level and 85% were concerned about developing thinking and memory problems as a result of their treatment (Fisher *et al.*, 2000).

As well as contributing to treatment failure, these perceived cognitive side effects can also have a considerable impact on day to day functioning and quality of life. Sixty-three per cent of respondents in the IBE Cognitive Function survey (2004) thought that AED cognitive effects had stopped them from achieving goals or activities, for example staying in education or following their chosen career. Therefore, avoiding adverse cognitive effects is an important consideration for many patients. When asked to rate areas of importance regarding their epilepsy medication, experiencing fewer side effects was ranked the second most important issue after seizure control (Fisher *et al.,* 2000).

Many patients attribute their cognitive impairments to the side effects of AEDs and neglect other potential causes, such as their underlying aetiology, recurrent seizures, or mood disturbance (Carpay *et al.,* 2005; Baker *et al.,* 2008). However, whilst 56% of patients associated their cognitive problems with their epilepsy medication in the IBE survey (2004), only 14% attributed their problems to their medication alone. The remaining 42% recognised that they were due to a combination of their condition and their medication.

Effects of AEDs on objective cognitive measures

All AEDs have the potential to affect cognitive function impacting on attention, vigilance and mental and psychomotor speed (e.g. Loring & Meador, 2001, Aldenkamp *et al.*, 2003). This is because they reduce seizures by decreasing neuronal irritability and suppressing epileptiform discharges, but this reduction in neuronal excitability may impair cognition (Motamedi & Meador, 2003, 2004, Loring *et al.,* 2007). Their cognitive side effects may be more pronounced in higher dosages and in polytherapy (e.g. Kwan & Brodie, 2001, Loring & Meador, 2001, Aldenkamp *et al.,* 2003, Mula & Trimble, 2009). In addition, some patients may be more susceptible to developing adverse cognitive events and identifying these patients is a currently an important and challenging area of research (Loring *et al.,* 2007).

Different AEDs may have different adverse effects; therefore, knowledge of their individual cognitive profiles is important, for both the patient and clinician, when selecting an AED. Yet, despite a wealth of studies and comprehensive reviews, our knowledge of the specific cognitive effects of individual drugs is still limited. This is mainly due to the methodological

shortfalls and differences between studies, which reduce confidence in the ability to make firm conclusions.

Methodological shortfalls of AED studies

Several authors have reviewed the limitations of studies in this area (e.g. Cochrane *et al.*, 1998, Loring *et al.,* 2007) and these are briefly summarised in Table 3.5. Shortfalls include small sample sizes; the use of tests not thought to be sensitive to detect AED effects; the use of brief exposure periods in healthy volunteer studies; the problems isolating specific AED effects in polytherapy studies; lack of appropriate comparison control groups; and failure to detail sufficiently methodology, design and analysis (Vermeulen & Aldenkamp, 1995). Differences between studies make comparing trials difficult and make it impossible to undertake systematic reviews and meta-analysis. These include differences in the populations studied; in the different time periods sampled; in the study designs; in the dosages and titration schedules, and in neuropsychological tests. Some of these shortfalls have been highlighted for over a decade, particularly, the lack of uniformity in selection of a neuropsychological test battery (Cochrane *et al.,* 1998, Baker & Marson, 2001).

Table 3.5: Methodological shortfalls and differences between randomised clinical trials investigating the cognitive side effects of AEDs

Methodological shortfall/difference	How it affects interpretability
Healthy volunteer studies	• Remove confounding effects (e.g. seizures, underlying aetiology) and provide information on AEDs that are prescribed for other conditions (e.g. gabapentin and pain; lamotrigine and anxiety) • Tend to have small sample sizes, brief drug exposure periods and may not be generalised to PWE
Add-on/polytherapy studies	• Cognitive side effects may occur due to interactions with other drugs or may be offset by better seizure control, making determining their specific effects more complex
Different patients studied (e.g. refractory or well-controlled)	• Results from one group may not be generalised or comparable with another group
Different designs (e.g. parallel-group, cross-over, single or double-blind)	• Cross-over studies may not have sufficient treatment periods to determine longer term effects • Absence of blinding may introduce bias
Different comparators (e.g. placebo, standard or new AEDs)	• Few head-to-head comparisons of newer AEDs means there is a lack of information when selecting a new AED
Lack of control groups	• Studies should include placebo controls (in add-on studies), untreated volunteers or those who have had seizures but have not been treated (in monotherapy studies) to assess absolute drug effects. • Lack of practice effect may be the first indicator of an AED effect
Small sample sizes	• Do not have adequate power to detect differences between drugs and many studies do not include power calculations so cannot determine whether study has sufficient power
Varying time intervals (e.g. days, weeks, months)	• AEDs may have differing effects acutely, during titration or during maintenance phase • Need more information on longer term effects
Varying dosages and titration schedules	• May have differing effects on cognitive function
Different or inadequate neuropsychological tests	• Tests may not be sensitive to the effects of AEDs or have not been standardised for use in PWE • Many studies have too many outcome measures (increasing chances of making a Type 1 error)
Failure to control for the effects of confounding variables (e.g. seizures, mood)	• Many studies do not control for effects of seizures or mood, making determining the specific effects of AEDs difficult • Those who do not achieve seizure reduction by an AED may drop out of the study and are not followed-up for assessment, introducing selection bias

Notwithstanding these shortfalls, there have been many comprehensive reviews of this area (e.g. Aldenkamp, 2001, Kwan & Brodie, 2001, Loring & Meador, 2001, Brunbech & Sabers, 2002, Motamedi & Meador, 2004, Loring *et al.*, 2007, Mula & Trimble, 2009). Therefore, the following section will only briefly review the cognitive side effects of AEDs. The review will be divided into the first, second and third generation drugs. Only evidence from randomised clinical trials (RCTs) will be included, as along with systematic reviews, these are considered to represent the 'gold standard' for evaluating the effects of treatments (Barton, 2000).

First generation AEDs

As the majority of studies involve comparisons between the older drugs (see Table 3.6), this section will be divided into the populations studied (e.g. healthy volunteers, patients with epilepsy) rather than a review of each individual drug.

Evidence from studies in healthy volunteers

Four studies have compared the cognitive side effects of the first generation AEDs in healthy volunteers (Thompson & Trimble, 1981, Meador *et al.*, 1991, 1993, 1995). Thompson & Trimble (1981) found that valproate was no different from placebo in a small (n=10), randomised, double-blind, cross-over study. Meador *et al.*, (1991) compared carbamazepine and phenytoin in 21 healthy adults in another randomised, double-blind, cross-over study. There were two significant differences between the drugs: carbamazepine was associated with improvement on a finger tapping task (measure of psychomotor speed) and phenytoin was associated with improvement on the Stroop task (measure of mental flexibility and inhibition of response). However, the authors noted that these differences were not clinically significant. Meador *et al.*, (1993) also found no differences between carbamazepine and phenytoin in a randomised, double-blind, cross-over study of 15 healthy adults. However, compared to a non-drug condition, both drugs were associated with impaired memory and mild EEG slowing. Similarly, phenobarbital, carbamazepine and phenytoin were worse than a non-drug condition on several cognitive measures, including memory, sustained attention and psychomotor speed in a later study by Meador *et al.*, (1995). However, phenobarbital was associated with poorer performance on measures of reaction time, interference, anger and concentration.

Table 3.6: Summary of RCTs investigating the cognitive side effects of first generation AEDs

Study	Date	AEDs	Design (monotherapy/ add-on)	Sample	Cognitive domains	Results
Dodrill & Troupin	1977	CBZ vs. PHT	Monotherapy	40 adult PWE	Intellectual functioning, memory, mental flexibility, language, psychomotor speed, emotional and social adjustment	No difference
Camfield *et al*	1979	PB vs. PBO	Monotherapy	65 children with FS	Intellectual functioning	No difference. PB associated with behavioural changes
Thompson & Trimble	1981	VPA vs. PBO	Monotherapy	10 healthy volunteers	Memory, concentration, perceptual speed, decision-making, motor speed, mood	No difference except VPA slower on decision-making
Mitchell & Chavez	1987	CBZ vs. PB	Monotherapy	33 CWE	Intellectual functioning, reasoning, behaviour	No difference
Smith *et al*	1987	PB vs. CBZ vs. PHT vs. PRM	Monotherapy	622 PWE; 75 healthy untreated controls	Intellectual functioning, attention, concentration, mental flexibility, motor manipulation, emotional and mood states	No difference but using a composite measure: PB and PHT sig deterioration. No practice effects in PWE.
Vining *et al*	1987	PB vs. VPA	Monotherapy	28 CWE	Intellectual functioning, memory and learning, reading, balance and co-ordination, psychomotor speed, vigilance and concentration, emotion and behaviour	PB < VPA on 4 tests (Performance measures, PIQ, FSIQ). Worse behaviour on PB
Farwell *et al*	1990	PB vs. PBO	Monotherapy	217 CWE; 150 healthy untreated controls	Intellectual functioning	After 2 years: IQ 8.4 points lower on PB. Six months after withdrawal, IQ 5.2 points lower than PBO.

Meador *et al*	1990	CBZ vs. PB vs. PHT	Monotherapy	21 PWE	Memory, attention, concentration, psychomotor speed, ERPs, mood	Few differences. PB < on digit symbol task
Forsythe *et al*	1991	CBZ vs. PHT vs. VPA	Monotherapy	64 CWE; 40 untreated controls (nocturnal enuresis or Migraine)	Intellectual functioning, memory, visual scanning, mental flexibility, speed of information processing, reading ability	Few differences. VPA>CBZ on memory
Meador *et al*	1991	CBZ vs. PHT	Monotherapy	21 healthy volunteers	Memory, sustained attention, mental flexibility, motor speed and co-ordination, ERPs, symptom checklist and mood	No clinically significant differences. CBZ > PHT (motor speed) and PHT>CBZ (mental flexibility) but AEDs < non-drug condition
Meador *et al*	1993	CBZ vs. PHT	Monotherapy	15 healthy volunteers	EEG, verbal memory task	No difference but AED < non-drug condition: impaired memory and mild EEG slowing.
Craig & Tallis	1994	VPA vs. PHT	Monotherapy	38 PWE	Memory, attention and concentration, information processing, psychomotor speed and co-ordination, mood, health profile questionnaire	No difference
Pulliainen & Jokelainen	1994	PHT vs. CBZ	Monotherapy	59 PWE; 21 healthy untreated controls	Motor speed and co-ordination, visual motor speed, attention and concentration, memory and learning, reason, mood	PHT < CBZ visual memory and motor speed. But reduction in practice effects (42% of variables for controls vs. CBZ 17% and PHT 4%)

Meador *et al*	1995	PHT vs. PB vs. VPA	Monotherapy	75 healthy adults	Psychomotor speed, ERPs, memory and learning, attention, mental flexibility, mood	PB < PHT and VPA on motor and mental flexibility tasks. All 3 < non-drug condition
Pulliainen & Jokelainen	1995	PHT vs. CBZ	Monotherapy	59 PWE	Motor speed and co-ordination, attention and concentration, memory and learning, reasoning, mood	No difference but improvement over time for 9 measures
Chen *et al*	1996	CBZ vs. PB vs. VPA	Monotherapy	76 CWE	Intellectual functioning, auditory ERPs	No difference
Prevey *et al*	1996	VPA vs. CBZ	Monotherapy	65 PWE; 72 healthy untreated controls	Intellectual functioning, motor speed and co-ordination, memory and learning, verbal fluency, mental flexibility, attention and concentration, emotional adjustment	No difference but lack of practice effect in PWE

CBZ= carbamazepine, PB= phenobarbital, PHT= phenytoin, PRM=primidone, VPA=valproate, PBO=placebo, PWE= people with epilepsy, CWE=children with epilepsy, FS=febrile seizures, PIQ= Performance IQ, FSIQ= Full Scale IQ, ERPs= event-related potentials, EEG=electroencephalogram

Evidence from studies in people with epilepsy

Eleven studies have investigated the cognitive-side effects of older AEDs in people with epilepsy (Dodrill & Troupin, 1977, Smith *et al.*, 1987, Mitchell & Chavez, 1987, Vining *et al.*, 1987, Meador *et al.*, 1990, Forsythe *et al.*, 1991, Craig & Tallis, 1994, Pulliainen & Jokelainen, 1994, 1995, Chen *et al.*, 1996, Prevey *et al.*, 1996). Eight of these have included people with newly diagnosed epilepsy (five in adults, three in children). Of the adult studies, Smith *et al.*, (1987), as part of a five-year randomised, double-blind, Veterans Administration study, compared carbamazepine, phenobarbital, phenytoin and primidone in 622 newly diagnosed, untreated patients with 75 healthy controls. They found no significant differences between drugs on each of the cognitive measures. However, when an overall composite score was calculated, carbamazepine had fewer effects than the other three drugs. Furthermore, they found that people with epilepsy were characterised by a lack of practice effect, which the authors suggested may be the first indicator of some AED effect. There was also a reduction in a normal practice effect in a randomised, partially-blinded, parallel-group study of carbamazepine and phenytoin involving 59 patients with newly diagnosed epilepsy compared with 21 healthy volunteers. After six months of treatment, the untreated healthy volunteers had a practice effect for 42% of variables; those randomised to carbamazepine 17% of variables, and those randomised to phenytoin 4% of variables (Pulliainen & Jokelainen, 1994). However, after two years, a follow-up study of this cohort revealed improvements across several measures and there were no differences between the drugs (Pulliainen & Jokelainen, 1995). Similarly, Prevey *et al.*, (1996) compared valproate and carbamazepine in a randomised, double-blind study of 65 newly diagnosed patients with symptomatic partial epilepsy and 72 healthy controls. This study also demonstrated that the AED group failed to show learning and practice effects and there were no differences between the two drugs. Likewise, after 12 months, there were few differences between valproate and phenytoin in a randomised, single-blind study of 38 newly diagnosed elderly patients (Craig & Tallis, 1994). Equally, two randomised, double-blind, cross-over studies in adults with epilepsy found few significant differences between carbamazepine, phenobarbital and phenytoin (Meador *et al.*, 1990) and carbamazepine and phenytoin (Dodrill & Troupin, 1977).

The studies from the paediatric literature also suggest that there are relatively few differences between these first generation AEDs. Two randomised, parallel-group studies in children with newly diagnosed epilepsy failed to find differences between carbamazepine and phenobarbital (Mitchell & Chavez, 1987) and carbamazepine, phenobarbital and valproate (Chen *et al.,* 1996). However, children with epilepsy treated with phenobarbital had a poorer Performance and Full Scale IQ compared with those treated with valproate in a double-blind, cross-over study by Vining *et al.,* (1987). And Forsythe *et al.,* (1991) found that after 6 and 12 months, scores on measures of memory functioning were better on valproate than carbamazepine in a randomised, single-blind study of 64 children with newly diagnosed epilepsy. However, there were no differences in measures of vigilance or concentration.

Two studies have compared phenobarbital and placebo in children with febrile seizures (Camfield *et al.*, 1979, Farwell *et al.*, 1990). After two years of treatment with phenobarbital, those randomised to phenobarbital had a mean IQ that was 8.4 points lower than the placebo group. Six months after withdrawal, their mean IQ was only 5.2 points lower than the placebo group, suggesting that this impairment was reversible (Farwell *et al.,* 1990). However, there were no differences in IQ between phenobarbital and placebo after 12 months of treatment in a randomised, double-blind, placebo-controlled study involving 65 toddlers. Phenobarbital was associated with increased fussiness and sleep disturbance, although parents could not distinguish between the two drugs; and only 21% correctly guessed that their child was randomised to phenobarbital (Camfield *et al.,* 1979).

Summary of the effects of the 1st generation AEDs

The majority of these studies have suggested that all the older AEDs have some effects on cognitive functioning. This may be reflected as either worse performance relative to a non-drug condition or a lack of normal practice effect. There are relatively few differences between the older AEDs, although phenobarbital has been associated with worse performance.

Second generation AEDs

The majority of studies of these newer AEDs have involved comparisons with placebo (see Table 3.7) or the established and standard AEDs (e.g. carbamazepine, valproate and

phenytoin) (see Table 3.8). Head-to-head comparisons between the newer drugs are relatively uncommon (see Table 3.9), which probably reflects the decision by the US Food and Drug Administration (FDA) in the early 1980s that new drugs had to demonstrate superiority in RCTs rather than equivalence. Many new studies compared the new drug with placebo rather than other therapies because of the difficulties in interpreting findings of noninferiority (Shorvon, 2009). This section will be divided into studies undertaken in each individual treatment.

Gabapentin

Five studies have investigated the cognitive side effects of gabapentin in healthy volunteers (Martin *et al.*, 1999, 2001, Meador *et al.*, 1999, Salinsky *et al.*, 2002, 2005). Three of the studies compared gabapentin with carbamazepine. Meador *et al.*, (1999) conducted a randomised, double-blind, cross-over study in 54 healthy participants. Across the neuropsychological test battery, gabapentin was associated with significantly better performance than carbamazepine on 26% of the variables. Both drugs produced effects on cognition, however, compared to a non-drug condition. But gabapentin had fewer effects, with worse performance on 27% of variables compared with 87% of variables on carbamazepine. Similar results were found in a randomised, double-blind, cross-over study in 35 healthy community-dwelling older adults (Martin *et al.*, 2001). Both drugs affected cognition, with gabapentin having fewer effects than carbamazepine compared with a non-drug condition (36% vs. 45%). There was only one significant difference between the two drugs on a measure of attention/vigilance. Salinsky *et al.*, (2002) also showed that those treated with gabapentin and carbamazepine performed differently to an untreated reference group on several cognitive measures in their randomised, double-blind, parallel-group study; but there were no differences between the two drugs.

Table 3.7: Summary of the RCTs comparing the cognitive side effects of the second generation AEDs with placebo

Study	Date	AEDs	Design (monotherapy/ add-on)	Sample	Cognitive domains	Results
Curran & Java	1993	OXC vs. PBO	Monotherapy	12 healthy volunteers	Memory and learning, verbal fluency, psychomotor speed, sustained attention, visuomotor co-ordination, EEG, mood and bodily symptoms scale	OXC > PBO on psychomotor speed and sustained attention but no difference on other measures
Dodrill *et al*	1993	VGB vs. PBO	Add-on	168 PWE	Intellectual functioning, motor speed and co-ordination, verbal fluency, mental flexibility, memory and learning, mood and adjustment	No difference
Gillham *et al*	1993	VGB vs. PBO	Add-on	24 PWE	Intellectual functioning, Psychomotor speed, memory and learning, general health questionnaire, AED side effects	No difference
Smith *et al*	1993	LTG vs. PBO	Add-on	81 PWE	Attention, psychomotor speed, mental flexibility	No difference
Grunewald *et al*	1994	VGB vs. PBO	Add-on	45 PWE	Intellectual functioning, memory and learning, mental speed and flexibility, cognitive flexibility, fluency, motor, mood and behaviour	VGB had reduction in motor speed and design learning
Sveinbjornsdottir *et al*	1994	TGB vs. PBO	Add-on	12 PWE	Memory and learning, mental flexibility, information processing, psychomotor speed, mood and behaviour	No difference

Dodrill *et al*	1995	VGB vs. PBO	Add-on	174 PWE	Intellectual functioning, mental flexibility, attention, motor speed and co-ordination, fluency, memory and learning, mood and adjustment	Decreases in performance with increasing doses of VGB on digit cancellation task (attention)
Kalviainen *et al*	1996	TGB vs. PBO	Add-on	43 PWE	Intellectual functioning, verbal fluency, memory and learning, EEG, attention and mental flexibility, motor speed	No difference
Provinciali *et al*	1996	VGB vs. PBO	Add-on	40 PWE	Adaptive abilities, memory and learning, mood and QOL	VGB improved in sustained attention, adaptive abilities and verbal learning
Thomas & Trimble	1996	VGB vs. PBO	Monotherapy	10 healthy volunteers	Memory, attention and concentration, mental flexibility, mood	No difference
Dodrill *et al*	1997	TGB vs. PBO	Add-on	247 PWE	Intellectual functioning, mental flexibility, attention, motor speed and co-ordination, fluency, memory and learning, mood and adjustment	No clinically significant changes with add-on TGB
Leach *et al*	1997	GBP vs. PBO	Add-on	27 PWE	Psychomotor, memory and learning, subjective well-being	No difference but learning improved on 2400mg GBP vs. PBO but reported more tiredness on this dose
Dodrill *et al*	1999	GBP vs. PBO	Monotherapy	201 PWE; 85 untreated reference group	Mental flexibility, attention, motor speed and co-ordination, fluency, memory and learning, mood and adjustment	No difference

Hindmarch *et al*	2005	PGB vs. PBO vs. APZ	Monotherapy	24 healthy volunteers	CNS arousal, vigilance, serial memory scanning, divided attention, reaction time, subjective sedation rating scales	No difference from PBO
Pressler *et al*	2006	LTG vs. PBO	Add-on	61 CWE	Memory, information processing, attention, behavioural ratings	No difference
Zhou *et al*	2008	LEV vs. PBO	Add-on	28 PWE	Intellectual functioning, verbal fluency, mental flexibility, attention, memory and QOL	LEV improved on 11% of variables, no improvements on PBO
Levisohn *et al*	2009	LEV vs. PBO	Add-on	99 CWE	Memory and learning, attention and concentration	No difference

GBP=gabapentin, LEV=levetiracetam, LTG=lamotrigine, OXC=oxcarbazepine, TGB=tiagabine, VGB=vigabatrin, PBO=placebo, APZ=alprazolam PWE=people with epilepsy, CWE=children with epilepsy, EEG=electroencephalogram, CNS=central nervous system

Table 3.8: Summary of the RCTs comparing the cognitive side effects of the second generation AEDs with first generation AEDs

Study	Date	AEDs	Design (monotherapy/ add-on)	Sample	Cognitive domains	Results
Aikia *et al*	1992	OXC vs. PHT	Monotherapy	37 PWE	Verbal learning and memory, sustained attention, psychomotor speed	No difference
Kalviainen *et al*	1995	VGB vs. CBZ	Monotherapy	100 PWE; 59 untreated patients single seizure	Verbal ability, verbal learning and memory, list learning, attention and mental flexibility	VGB improved vs. untreated and CBZ in verbal fluency, VGB and untreated improved vs. CBZ on delayed memory and mental flexibility and CBZ slowed for motor speed
Meador *et al*	1999	GBP vs. CBZ	Monotherapy	54 healthy volunteers	Attention and vigilance, cognitive and motor and speed, memory, mental flexibility, mood and symptom checklist	GBP> CBZ on 26% of variables; CBZ < non-drug 87%, GBP < non-drug 27%
Aldenkamp *et al*	2000	TPM vs. VPA	Add-on (to CBZ)	59 PWE	Psychomotor speed, information processing, memory and learning, mood and subjective side effects	TPM<VPA on verbal memory and learning
Dodrill *et al*	2000	TGB vs. CBZ/PHT	Add-on (to CBZ/PHT)	277 PWE	Intellectual functioning, mental flexibility, attention, motor speed and co-ordination, fluency, memory and learning, mood and adjustment	No difference between TGB vs. PHT when added to CBZ. TGB>CBZ on verbal fluency and motor speed when added to PHT

Martin *et al*	2001	GBP vs. CBZ	Monotherapy	34 healthy volunteers	Memory, language, verbal fluency, motor speed and co-ordination, sustained attention, mood	GBP>CBZ 6% (attention/vigilance), CBZ<non-drug 45%, GBP <non-drug 36%
Meador *et al*	2001	LTG vs. CBZ	Monotherapy	36 healthy volunteers	Attention/vigilance, cognitive and motor speed, memory, moor, subjective behavioural measures	LTG>CBZ 48% of variables; CBZ<non-drug 62%, LTG<non-drug 2.5%
Aldenkamp *et al*	2002a	LTG vs. VPA vs. PBO	Monotherapy	30 healthy volunteers	Psychomotor speed, information processing, memory and learning, mood, subjective complaints	LTG > VPA and PBO on cognitive activation and alertness
Salinsky *et al*	2002	GBP vs. CBZ	Monotherapy	30 healthy volunteers; 72 untreated reference group	Psychomotor speed, mental flexibility, memory and learning, mood	No difference but AED groups declined in performance vs. untreated reference group.
Meador *et al*	2003	TPM vs. VPA vs. PBO	Add-on (to CBZ)	76 PWE	Attention/vigilance, psychomotor speed, memory, fluency, mood and QOL	TPM<VPA on visual scanning and verbal fluency
Salinsky *et al*	2004	OXC vs. PHT	Monotherapy	32 healthy volunteers; 73 untreated reference group	Attention/vigilance. Psychomotor speed, mental flexibility, memory and learning, mood and subjective complaints	No difference but AEDs declined vs. untreated reference group on 25% of variables (mainly motor speed)

Aikia *et al*	2006a	TGB vs. CBZ	Monotherapy (pooled analysis)	105 PWE; 19 untreated patients single seizure	Memory and learning, mental flexibility, attention, verbal fluency, psychomotor speed	No difference TGB vs. CBZ. One significant difference CBZ<untreated group on verbal fluency
Donati *et al*	2006	OXC vs. CBZ vs. VPA	Monotherapy	112 CWE	Psychomotor speed, information processing, memory and learning, reasoning	No difference
Meador *et al*	2007	LEV vs. CBZ	Monotherapy	28 healthy volunteers	Sustained attention, memory, mental flexibility, motor speed and co-ordination, mood, QOL and subjective self-report	LEV>CBZ on 44% of variables; CBZ < non-drug 76%; LEV<non-drug 12%

CBZ=carbamazepine, GBP=gabapentin, LEV=levetiracetam, LTG=lamotrigine, OXC=oxcarbazepine, PHT=phenytoin, TGB=tiagabine, TPM=topiramate, VPA=valproate, VGB=vigabatrin, PBO=placebo, PWE=people with epilepsy, CWE=children with epilepsy, QOL=quality of life

Table 3.9: Summary of the RCTs comparing the cognitive side effects of second generation AEDs

Study	Date	AEDs	Design (monotherapy/add-on)	Sample	Cognitive domains	Results
Martin *et al*	1999	TPM vs. LTG vs. GBP	Monotherapy	17 healthy volunteers	Attention, memory, verbal fluency, object naming mood	TPM<GBP and LTG on verbal fluency and visual attention at acute phase. TPM declined on verbal memory and psychomotor speed
Fritz *et al*	2005	TGB vs. TPM	Add-on	41 PWE	Premorbid IQ, handedness, mental flexibility, memory and learning, fluency, psychomotor speed, language, mood	Baseline to titration: TPM declined in verbal fluency, language comprehension, working memory. TGB declined in verbal memory. Functions stable in maintenance phase.
Meador *et al*	2005	LTG vs. TPM	Monotherapy	75 healthy adults	Sustained attention, memory and learning, verbal fluency, language, motor speed and co-ordination, mood and subjective complaints	LTG>TPM on 80% variables. TPM<non-drug 88%, LTG<non-drug 17%
Salinsky *et al*	2005	TPM vs. GBP vs. PBO	Monotherapy	40 healthy volunteers; 73 untreated reference group	Motor speed and co-ordination, sustained and divided, attention, mental flexibility, memory and learning, verbal fluency, mood and subjective side effects	No difference GBP vs. PBO. TPM<GBP and PBO on 67% of target variables. TPM effects large >2SD change.

Blum *et al*	2006	LTG vs. TPM	Add-on (to CBZ/PHT)	193 PWE	Verbal fluency, mental flexibility, attention, motor speed and co-ordination, memory and learning, performance on-line task (driving simulator), subjective side effects	LTG>TPM on a composite measure. LTG>TPM on fluency, mental flexibility, attention and driving simulator task. Some of these tasks were clinically significant differences

CBZ=carbamazepine, GBP=gabapentin, LTG=lamotrigine, PHT=phenytoin, TGB=tiagabine, TPM=topiramate, PBO=placebo, PWE=people with epilepsy, SD=standard deviation

Martin *et al.,* (1999) compared gabapentin with lamotrigine and topiramate in a randomised, single-blind, parallel-group study in 17 healthy young adults, of which only 11 completed the trial. They found significant differences between the drugs with topiramate having worse performance than gabapentin and lamotrigine on measures of verbal fluency and visual attention at an acute dosing phase. After four weeks of treatment, topiramate was associated with poorer performance on measures of verbal memory and psychomotor speed. Consistent with this, Salinsky *et al.,* (2005) carried out a randomised, double-blind, parallel-group study comparing gabapentin with topiramate and placebo in 40 healthy volunteers with an untreated reference group. Gabapentin did not differ from placebo on six target measures but was significantly better than topiramate on four of the six measures (digit symbol, story recall, selective reminding, controlled oral word association).

Only two studies have investigated the cognitive side effects of gabapentin in people with epilepsy (Leach *et al.*, 1997, Dodrill *et al.*, 1999). Leach *et al.,* (1997) compared add-on gabapentin with placebo in patients with refractory epilepsy in a randomised, double-blind, dose-ranging, placebo-controlled, cross-over study. There was no effect of gabapentin on composite memory or psychomotor scores. There was also no change in subjective reports, although those on the highest dosage (2400mg) complained of increased tiredness. Similarly, no cognitive changes were associated with gabapentin monotherapy treatment in patients with refractory epilepsy in a randomised, double-blind, parallel-group, dose-controlled study compared with placebo. However, after 26 weeks of treatment, those randomised to receive lower dosages (600mg) reported improved mood and psychosocial adjustment (Dodrill *et al.,* 1999).

Lamotrigine

Three studies have investigated the cognitive side effects of lamotrigine in healthy volunteers (Martin *et al.,* 1999, Meador *et al.*, 2001, Aldenkamp *et al.*, 2002a). Meador *et al.* (2001) compared lamotrigine with carbamazepine in a randomised, double-blind, cross-over study. Lamotrigine was associated with better performance than carbamazepine on 48% of variables. It was only worse than a non-drug condition on 2.5% of variables, compared with carbamazepine, which was worse on 62% of variables. This suggests that lamotrigine has

fewer adverse effects than carbamazepine. Aldenkamp *et al.*, (2002a) has also found improvements in cognitive activation and alertness associated with lamotrigine treatment compared with valproate and placebo in a randomised, double-blind, parallel-group design. In addition, those on lamotrigine reported fewer cognitive complaints than those on valproate and also reported an improvement in mood. As discussed in the previous section, there were fewer adverse effects for lamotrigine compared with topiramate in the study by Martin *et al.*, (1999). This has also been reported in other studies comparing lamotrigine and topiramate (e.g. Meador *et al.*, 2005, Blum *et al.*, 2006) but these will be discussed in a later section (see Topiramate).

Only two studies have considered the cognitive effects of lamotrigine in people with epilepsy (Smith *et al.*, 1993, Pressler *et al.*, 2006). Both studies compared add-on lamotrigine with placebo. Smith *et al.*, (1993) conducted a randomised, double-blind, cross-over study in 81 patients with refractory partial seizures. There were no differences between lamotrigine and placebo on any of the measures, suggesting that lamotrigine is not associated with impairment of attention, concentration, motor speed or repetitive mental activity. There were also no differences from placebo in a study with the same design involving 61 children with well-controlled or mild epilepsy by Pressler *et al.*, (2006).

Levetiracetam

A randomised, double-blind cross-over study by Meador *et al.*, (2007) has investigated the cognitive effects of levetiracetam compared with carbamazepine in 28 healthy adults. Across the neuropsychological test battery, levetiracetam was associated with significantly better performance than carbamazepine on 44% of variables. Compared to a non-drug condition, carbamazepine was significantly worse on 76% of variables but levetiracetam was only worse on 12% of variables. This suggests that levetiracetam has a more favourable cognitive profile than carbamazepine.

Two studies have compared add-on levetiracetam with placebo in people with epilepsy (Zhou *et al.*, 2008, Levisohn *et al.*, 2009). Zhou *et al.*, (2008) carried out a short-term, randomised, double-blind, placebo-controlled study in 28 people with refractory seizures, followed by a

long-term open-label study, where all patients were treated with levetiracetam. In the short-term study (16 weeks treatment period) those treated with levetiracetam demonstrated improvements on 11% of variables while those administered placebo had no improvements. In the long-term study (24 weeks treatment period) 53% of variables improved from baseline. Those who had changed to levetiracetam from placebo had improvements on 32% of variables. A randomised, double-blind, placebo-controlled study in children with refractory epilepsy did not find any improvements but did not find any differences between levetiracetam and placebo, again suggesting that levetiracetam is not associated with negative effects on cognition (Levisohn *et al.*, 2009).

Oxcarbazepine

Two studies have investigated the cognitive side effects of oxcarbazepine in healthy volunteers (Curran & Java, 1993, Salinsky *et al.*, 2004). Curran & Java (1993) compared oxcarbazepine and placebo over a two week treatment period in a small (n=12) randomised, double-blind, cross-over study. There were no differences between oxcarbazepine and placebo on measures of memory. However, when treated with oxcarbazepine, participants improved their performance on a digit cancellation task (measure of psychomotor speed and sustained attention) and were able to copy more symbols on a symbol copying task (measure of psychomotor speed, sustained attention, response speed, visuomotor coordination and incidental memory). They also rated themselves as being more alert, quick-witted and clear-headed and this was dose-related. Those on higher doses reported experiencing more symptoms of palpitations and trembling. Salinsky *et al.*, (2004) compared oxcarbazepine with phenytoin in 32 healthy volunteers and an untreated reference group in a randomised, double-blind, parallel-group study. After 12 weeks, treatment with AEDs was associated with worse performance on 25% of variables, particularly, those measuring motor speed and reaction time. However, these were modest effects, representing a change of less than one standard deviation. There were no differences between oxcarbazepine and phenytoin on the cognitive measures, but those randomised to phenytoin reported more subjective problems in mood and symptoms of neurotoxicity.

Three studies have considered the cognitive side effects of oxcarbazepine in people with newly diagnosed epilepsy (Aikia *et al.*, 1992, Donati *et al.*, 2006, 2007). Aikia *et al.*, (1992) compared oxcarbazepine and phenytoin in 37 adults in a randomised, double-blind, parallel-group study. There were no differential effects between the two drugs. Similarly, Donati *et al.*, (2006, 2007) found oxcarbazepine did not differ from carbamazepine or valproate in a randomised, open-label, parallel-group study involving 112 children and adolescents with partial epilepsy. However, the data presented in the two studies by Donati *et al.*, (2006, 2007), appears to be the same, so this should be taken to represent only one piece of evidence.

Pregabalin

Despite being first licensed for use in the UK in 2004, only one randomised clinical trial has investigated the cognitive effects of pregabalin. Hindmarch *et al.*, (2005) compared pregabalin to placebo and alprazolam (used for the short-term treatment of moderate or severe anxiety and anxiety associated with depression) in 24 healthy volunteers. Pregabalin did not seem to affect cognitive functioning. The authors concluded that the drug would have a generally benign CNS side effects profile in clinical use. However, studies in people with epilepsy are needed to support this finding.

Tiagabine

Six studies have investigated the cognitive side effects of tiagabine in people with refractory epilepsy (Sveinbjornsdottir *et al.*, 1994, Kalviainen *et al.*, 1996, Dodrill *et al.*, 1997, 1998, 2000, Fritz *et al.*, 2005). Three of these studies compared add-on tiagabine to placebo. Sveinbjornsdottir *et al.*, (1994) conducted an initial open trial of add-on tiagabine in 22 adults with refractory epilepsy followed by a randomised, double-blind, placebo-controlled, cross-over study in 12 patients who had responded to the drug. There were no differences on any of the cognitive measures compared with placebo in either study, although two relatives reported that they had noticed improvements while the patients were on tiagabine. Similarly, Kalviainen *et al.*, (1996) reported no differences between add-on tiagabine and placebo in a randomised, double-blind, parallel-group study in 43 patients with chronic epilepsy. But there were significant improvements on a list learning task and in auditory reaction time after 6-24 months of an open-label extension study. The lack of difference between the drug and placebo is

supported by data from a large (n=162), randomised, double-blind, parallel-group, dose-response study undertaken by Dodrill *et al.,* (1997). They found no clinically significant changes between add-on tiagabine and placebo over a 12 week treatment period.

Two studies have compared add-on tiagabine to other AEDs used as adjunctive therapy (Dodrill *et al.,* 2000; Fritz *et al.,* 2005). There were no differences between add-on tiagabine and phenytoin when added to carbamazepine in a randomised, double-blind study of 277 patients with refractory partial seizures undertaken by Dodrill *et al.,* (2000). However, there were differences between add-on tiagabine and carbamazepine when added to phenytoin. Add-on tiagabine was associated with improvements in verbal fluency and motor speed. In contrast, add-on tiagabine was associated with deteriorations in verbal memory in a randomised, open-label, parallel-group study of 41 patients with refractory epilepsy. However, these deteriorations were only noted in the titration phase and functions remained stable during the three month maintenance phase (Fritz *et al.,* 2005).

A randomised, double-blind, parallel-group study in 123 adults with refractory partial seizures has considered the cognitive effects of differing dosages of tiagabine monotherapy. Patients were randomised to receive 6 mg or 36 mg/day. There were few changes in cognitive abilities, adjustment or mood (Dodrill *et al.,* 1998). One further study has investigated tiagabine monotherapy in people with newly diagnosed epilepsy (Aikia *et al.*, 2006a). Aikia *et al.,* (2006a) carried out a pooled analysis of two studies comparing tiagabine with carbamazepine in 105 patients with newly diagnosed epilepsy and 19 patients who only had one seizure but were not treated with AEDs. The authors concluded that tiagabine had a similar cognitive profile to carbamazepine and to the untreated patients.

Topiramate

Three studies have investigated the cognitive side effects of topiramate in healthy volunteers (Martin *et al.,* 1999, Meador *et al.,* 2005, Salinsky *et al.,* 2005). As discussed in a previous section (gabapentin), Martin *et al.,* (1999) and Salinsky *et al.,* (2005) have found poorer performance associated with topiramate compared with other newer AEDs, such as lamotrigine and gabapentin. In the study by Salinsky *et al.,* (2005), the negative effects

associated with topiramate treatment were large. Several tests had changes of more than two standard deviations (considered to be clinically significant) and more than half of the participants had a test-retest change of this magnitude for measures of verbal fluency, verbal memory and psychomotor speed. Similarly, another healthy volunteer study found worse cognitive performance with topiramate compared to lamotrigine. Meador *et al.,* (2005) conducted a randomised, double-blind, cross-over study in 75 healthy volunteers. After 12 weeks, lamotrigine was significantly better than topiramate on 80% of variables, including measures of attention and vigilance, memory, language and mental and motor speed. Topiramate was not better than lamotrigine on any of the variables. Both drugs affected cognition compared with a non-drug condition; but the non-drug condition was only better than lamotrigine for 17% of variables compared with 88% of variables for topiramate. A related study by Werz *et al.*, (2006) found that 70% of the healthy volunteers from this study preferred lamotrigine and only 16% preferred topiramate.

Five studies have investigated the cognitive side effects of topiramate in people with epilepsy (Aldenkamp *et al.*, 2000, Meador *et al.*, 2003, Fritz *et al.,* 2005, Blum *et al.,* 2006, Lee *et al.*, 2006). Four studies have compared add-on topiramate to adjunctive treatment with other AEDs. Aldenkamp *et al.,* (2000) undertook a randomised, observer-blinded, parallel-group study comparing add-on topiramate with valproate in 59 patients with partial onset seizures already on carbamazepine treatment. After 20 weeks of treatment, a higher proportion of patients randomised to topiramate dropped out of the study, often due to cognitive complaints. However, there were few differences between the two drugs. The only significant difference was on a measure of memory functioning, with topiramate associated with worse scores. A higher proportion of those randomised to topiramate also dropped out of a randomised, double-blind, placebo-controlled, parallel-group study of 76 patients with refractory epilepsy by Meador *et al.* (2003). They compared add-on topiramate to valproate and placebo. Topiramate was associated with poorer performance on a measure of verbal fluency and on a symbol digit modalities test (measure of complex scanning and visual tracking). However, the authors noted that it was a small subset of patients that appeared to be more negatively affected.

These studies suggest that language-related functions seem to be vulnerable to the effects of topiramate. Two further add-on studies have also demonstrated adverse effects on these functions, particularly, verbal fluency. Fritz *et al.,* (2005) compared add-on topiramate to add-on tiagabine in 41 patients with intractable epilepsy. Those on topiramate reported more concerns about their cognitive functioning and performed worse on measures of verbal fluency, language comprehension and working memory. A randomised, double-blind, parallel-group study in 193 adults with partial epilepsy by Blum *et al.,* (2006) also found that performance on verbal fluency and the symbol digit modalities test exceeded the minimum clinically important difference in the topiramate group. In a related study from the same cohort, performance on a driving simulator task, which measures scanning, divided attention and the effective field of view, was compromised by add-on topiramate therapy (Mills *et al.*, 2008).

One study has considered the effects of different doses (50, 75, 100mg) of topiramate monotherapy in a randomised, open study of 47 patients with newly diagnosed epilepsy. After 12 months of treatment, 44% of patients complained of cognitive problems. Of these, 42% complained of memory deficits, 25% of speech problems, 11% of attention and concentration and 6% of psychomotor slowing. Performance on tasks of verbal fluency and working memory decreased after 12 months and higher dosages were associated with greater declines. Twelve patients withdrew from topiramate over the course of the study because of their cognitive deficits. After withdrawal, their scores on working memory and verbal fluency increased, suggesting that these are transient, reversible, medication-related deficits (Lee *et al.,* 2006).

Vigabatrin

One study has investigated the cognitive side effects of vigabatrin in healthy volunteers (Thomas & Trimble, 1996). Thomas & Trimble (1996) conducted a randomised, double-blind, cross-over study comparing add-on vigabatrin and placebo in ten healthy volunteers. After a two week treatment period, there were improvements in a measure of information processing and no changes on any other cognitive measure.

Five studies have compared add-on vigabatrin with placebo in patients with refractory epilepsy (Dodrill *et al.,* 1993, 1995, Gillham *et al.*, 1993, Grunewald *et al.*, 1994, Provinciali *et*

al., 1996). There were no differences between adjunctive vigabatrin and placebo on any measure of cognition, mood or adjustment in a randomised, double-blind, parallel-group study of 168 patients with refractory partial epilepsy conducted by Dodrill *et al.*, (1993). Equally, there were no differences between add-on vigabatrin and placebo in a randomised, double-blind, cross-over study in 24 patients with refractory epilepsy (Gillham *et al.*, 1993). However, in a follow-on study of 12 patients who had responded to the drug, there were improvements in three psychomotor tests, four memory tests and three self-rating scales, measuring general health, sedation and subjective side effects, after 14.75 months of treatment. Similarly, there were improvements in sustained attention, adaptive abilities and verbal learning after four months of adjunctive treatment with vigabatrin in a randomised, single-blind, parallel-group study of 40 patients with refractory complex partial seizures (Provinciali *et al.*, 1996). In contrast, Grunewald *et al.*, (1994) found a significant reduction in motor speed and design learning associated with add-on vigabatrin in a randomised, double-blind, parallel-group study but no evidence of further decline after long-term treatment (up to 18 months). The authors suggested that this may have been due to a pre-existing impairment caused by their refractory partial seizures. Finally, Dodrill *et al.*, (1995) found poorer performance on a digit cancellation task as vigabatrin dosages increased (1g, 3g, 6g) in a randomised, parallel-group, placebo-controlled, dose-response study in 174 patients with refractory partial epilepsy but did not find dose-related changes on any other measures.

One study undertaken by Kalviainen *et al.*, (1995) has compared vigabatrin monotherapy with carbamazepine monotherapy in 100 patients with newly diagnosed epilepsy and 50 patients with a single seizure who were not treated with AEDs. After 12 months, those randomised to vigabatrin treatment and the untreated patients improved on a measure of attention and mental slowing. Those on vigabatrin compared with those on carbamazepine and those who were untreated improved on a measure of verbal fluency. This suggests that vigabatrin is not associated with adverse effects on cognition.

Zonisamide

Despite being first licensed for use in the UK in 2005, only one randomised clinical trial has investigated the cognitive side effects of zonisamide. Park *et al.*, (2008) carried out a

randomised, open-label study investigating different dosages (100, 200, 300, 400 mg/day) of zonisamide in 43 patients with newly diagnosed epilepsy. Nine patients withdrew before the end of the 12 month treatment period, three because of cognitive and mood problems. Forty-seven per cent of patients complained of cognitive deficits, particularly, memory impairments and attention and concentration problems, particularly on higher doses. On objective measures of cognitive functioning, there were declines on measures of verbal and visual memory, working memory, mental flexibility and verbal fluency, and these were dose-related.

Third generation AEDs

Table 3.10 summarises the only study that has so far been undertaken to investigate the cognitive side effects of the third generation AEDs.

Table 3.10: Summary of RCTs investigating the cognitive side effects of third generation AEDs

Study	Date	AEDs	Design	Sample	Cognitive domains	Results
Aldenkamp & Alpherts	2006	RUF vs. PBO	Add-on	213 PWE	Psychomotor speed, information processing, memory	No difference

RUF=rufinamide, PBO=placebo, PWE= people with epilepsy

Lacosamide

Lacosamide was first licensed for use in the UK in 2008. To date, there have been no published randomised clinical trials of lacosamide that have included measures of cognitive function.

Rufinamide

Rufinamide is a relatively new drug that was first licensed for use in the UK in 2007. Only one randomised clinical trial has investigated its cognitive effects. Aldenkamp & Alpherts, (2006) conducted a large, double-blind, parallel-group study of four dosages of adjunctive rufinamide (200, 400, 800, 1600mg/day) compared with placebo in 189 patients with partial seizures. There were no significant deteriorations on any of the cognitive measures and no differences

between the four rufinamide dose groups and placebo. This suggests that there were no cognitive effects associated with rufinamide even at higher dosages.

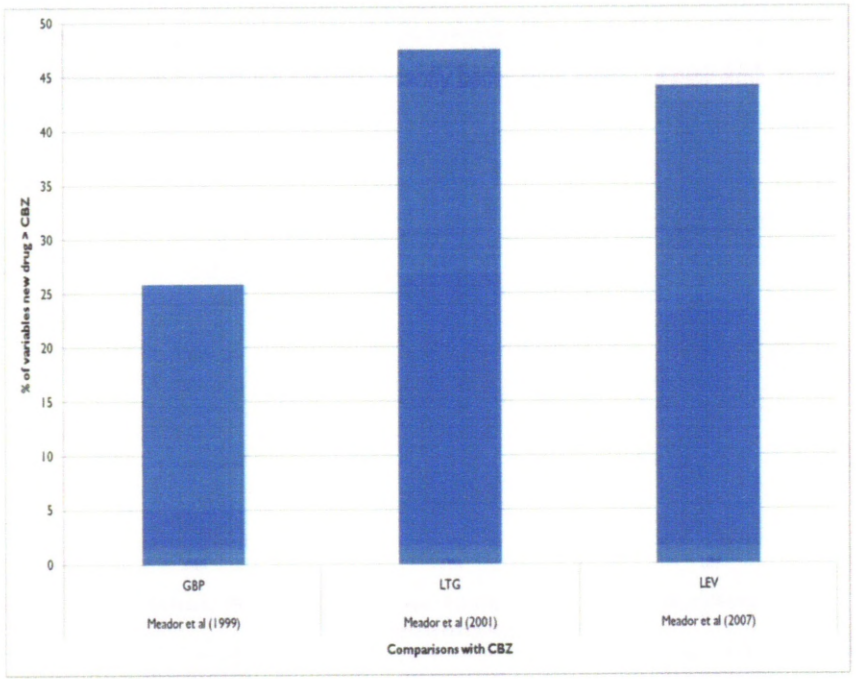
Summary of the effects of the second and third generation AEDs

The studies that have been conducted so far suggest that these newer AEDs have similar or more favourable cognitive profiles than the older more established AEDs. However, problems with verbal fluency, verbal memory, working memory, attention and language have been associated with topiramate and more recently zonisamide. Lamotrigine, gabapentin and levetiracetam seem to produce fewer adverse effects compared with the standard AEDs (e.g. carbamazepine). But all of these still affect cognition. Their more favourable cognitive profile is nicely illustrated in a series of randomised, double-blind, cross-over healthy volunteer studies conducted by Meador and colleagues (1991, 1995, 2001). As illustrated in Figure 3.4, all of the newer AEDs (gabapentin, lamotrigine and levetiracetam) performed better than carbamazepine across a neuropsychological test battery. Lamotrigine was significantly better on nearly half the cognitive measures (see Figure A). However, all the AEDs produced cognitive effects relative to a non-drug condition but the newer AEDs, produced fewer cognitive effects than carbamazepine. Lamotrigine was only significantly worse than the non-drug condition on 2.5% of variables (see Figure B).

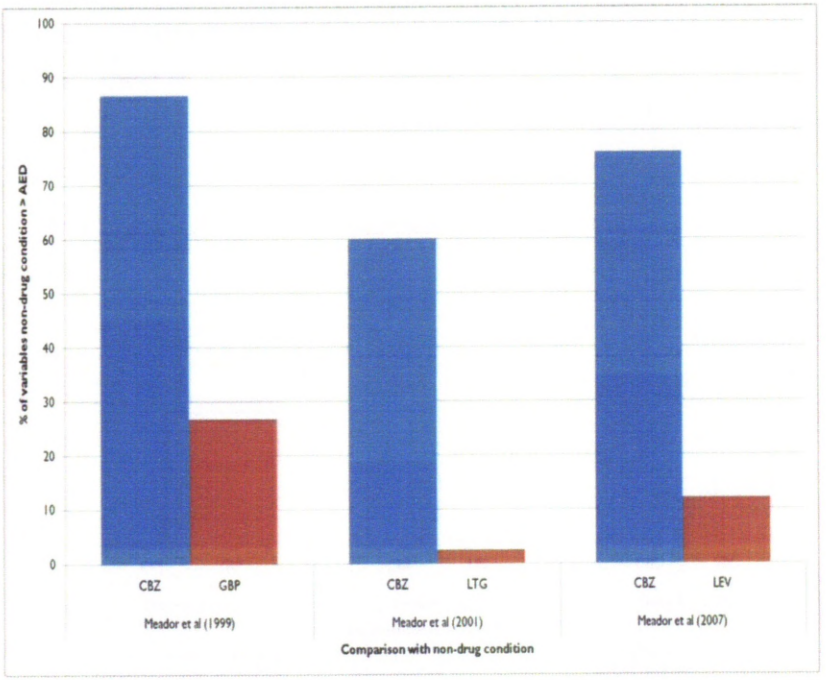
There is still a paucity of data on the neuropsychological effects of some of the more recently licensed AEDs, especially, lacosamide, pregabalin, rufinamide and zonisamide. Future studies need to be conducted on these drugs, taking into account the methodological shortfalls with previous work in this area.

Figure 3.4: Figure A illustrates the proportion of variables where the new drug was significantly better than carbamazepine. Figure B illustrates the proportion of variables where the non-drug condition was significantly better than either the new AED or carbamazepine

A



B



Summary of the effects of AEDs on cognition

People with epilepsy frequently report experiencing cognitive side effects as a result of their AED treatment. As a consequence of their mechanisms of action, all AEDs produce adverse cognitive effects, particularly, memory impairments, attention problems and mental and motor slowing (e.g. Meador *et al.*, 1993, 1995). These effects can be more pronounced at above therapeutic dosages or in polytherapy. Many patients will need to balance the benefits of reduced seizures with the negative effects of AEDs. However, their effects are relatively modest, especially when compared to the disease itself (Loring *et al.*, 2007). Their effects may be more clinically significant when crucial functions are involved, such as learning ability in children; vigilance when driving in adults, or when they impact on pre-existing age-related cognitive deficits in older adults (Aldenkamp, 2001).

Despite 25-30 years of research documenting the cognitive side effects of AEDs, no definitive conclusions on the impact of individual drugs have been drawn. This is mainly due to the methodological shortfalls of many previous studies and the difficult in isolating the effects of AEDs from the effects of other factors, such as the underlying aetiology, effects of seizures or mood.

However, the studies that have been conducted so far suggest that, in terms of their individual profiles, there are few differences between the older AEDs (though phenobarbital is considered to have a more detrimental impact on cognition). Few comparisons between the newer AEDs have been carried out but the majority seem to have a more favourable cognitive profile than the older AEDs (see Table 3.11). However, topiramate and zonisamide have been associated with language-related problems, although the risk may be decreased with slower titration rates and lower doses.

Understanding the cognitive side effects of AEDs is an important area of research that warrants further investigation, particularly as treatment-related side effects are one of the causes that is potentially avoidable by appropriate monitoring or changing therapy (Loring *et al.*, 2007).

Table 3.11: Cognitive side effects of individual AEDs (adapted from Hamed, 2009)

Generation	AED	Effect on cognition
1st	Phenobarbital	+++
	Phenytoin	+
	Carbamazepine	+
	Valproate	++
2nd	Gabapentin	0
	Lamotrigine	0
	Levetiracetam	0
	Oxcarbazepine	++
	Pregabalin	?
	Tiagabine	0
	Topiramate	+++
	Vigabatrin	0
	Zonisamide	+
3rd	Lacosamide	?
	Rufinamide	?

+++ deleterious negative effect; ++ modest negative effect, + mild negative effect, 0 little or negligible negative effect, ? unknown (not enough information)

Epilepsy surgery

As this thesis aims to explore the 'natural history' of cognitive functioning in people with epilepsy, those who have undergone intervening epilepsy surgery will not be included in the longitudinal studies reported in Chapter 7 and Chapter 8. Therefore, this section will only briefly consider the cognitive side effects of epilepsy surgery.

A recent review by Baxendale (2008) on the impact of epilepsy surgery on cognition and behaviour found that there have been more than 100 studies investigating cognitive outcomes following surgery. These have mainly been published during the last 15 years (Tellez-Zenteno & Wiebe, 2008). The majority of these have focused on memory functioning. Following epilepsy surgery, there is a risk of deterioration in verbal memory abilities, particularly if the resection is in the language-dominant hemisphere. However, verbal memory and intellectual functioning is relatively stable or improves following right temporal lobe resection (Spencer & Huh, 2008). Those who are rendered seizure free often also have a better cognitive outcome (e.g. Selwa *et al.*, 1994, Jokeit & Ebner, 1999, Helmstaedter *et al.*, 2003). For example, in the study by Jokeit & Ebner (1999) those who were seizure free six months after anterior temporal

lobectomy had a small but statistically significant improvement in Full Scale IQ compared with those who continued to have seizures. Helmstaedter *et al.*, (2003) in their longitudinal study concluded that surgically treated patients were either 'double winners' (seizure free and had cognitive stability or recovery) or 'double losers' (continue to have seizures and cognitive decline). Seizure control was an important determinant of cognitive prognosis. However, the majority of surgery studies only have short follow-up intervals and Baxendale (2008) commented that '*despite the burgeoning outcome literature, we still know relatively little about the long term outcomes of epilepsy surgery*'. In support of this, a recent systematic review only identified seven surgical studies that reported long-term (i.e. more than five years) neuropsychological outcomes. These outcomes are similar to those from short-term follow-up studies (Tellez-Zenteno *et al.*, 2007).

The majority of studies reporting cognitive outcomes after surgery are group studies but importantly there are individual variations between people with epilepsy. Up to a third may experience a decline in memory functioning postsurgically but approximately 10-20% may experience a postoperative improvement (Baxendale *et al.*, 2008a). Therefore, knowledge and understanding of which patients may be most at risk of developing cognitive decline is important when assessing suitability for surgery and counselling patient's so they can make an informed decision.

Several studies have evaluated the risk of experiencing cognitive decline from preoperative demographic and clinical factors. Predictors of poor cognitive outcome are illustrated in Table 3.12, although some of the evidence for these predictors is inconsistent. For example, a study by Potter *et al.*, (2009) showed that presurgical cognitive ability was a significant and positive predictor of postsurgical ability and having higher preoperative verbal or visual skills predicts good cognitive outcomes after anterior temporal lobectomy. The authors suggest that this fits with the cerebral reserve hypothesis that those who have a greater cognitive reserve can withstand greater brain insults (e.g. Stern, 2002). However, others have suggested that high preoperative cognitive performance is a predictor for poor postsurgical cognitive outcome (Meador, 2002, Spencer & Huh, 2008). Consequently, further research is needed to allow clinicians to more accurately predict which patients are at risk.

Table 3.12: Predictors of poor cognitive outcome following epilepsy surgery (Meador, 2002, Spencer & Huh, 2008)

Predictors of poor cognitive outcome
• High preoperative cognitive performance
• MRI lesion other than mesial temporal lobe sclerosis
• Absence of ipsilateral hippocampal atrophy/sclerosis
• Mesial temporal sclerosis on the side contralateral to be resected
• Greater functional adequacy of the temporal lobe to be resected
• Resection of the language dominant hemisphere
• Longer duration of epilepsy
• Younger age at surgery

In a clinical setting, the Wada test is often used to assess the risk of developing a postoperative amnesic syndrome and assess language lateralisation in those being considered for temporal lobe surgery. However, its usefulness and necessity has been debated (e.g. Loring, 2008, Jones-Gotman, 2008, Baxendale *et al.*, 2008b). An increasing number of centres are now using fMRI and the results of baseline neuropsychological testing, along with clinical information (e.g. side and type of surgery) rather than the Wada test in the prediction of cognitive outcome (Helmstaedter, 2008).

Vagal nerve stimulation

There have been relatively few studies conducted on the cognitive side effects of vagal nerve stimulation. Three studies have suggested that there are no cognitive changes associated with long-term VNS treatment in both children and adults with epilepsy (Dodrill & Morris, 2001, Hoppe *et al.*, 2001, Hallbook *et al.*, 2005). In contrast, others have suggested improvements in memory following VNS (Liebman *et al.*, 1998, Clark *et al.*, 1999, Ghacibeh *et al.*, 2006). Clark *et al.*, (1999) found that participants had better memory retention for highlighted nouns in emotionally neutral paragraphs after VNS. Ghacibeh *et al.*, (2006) concluded in their experimental study that VNS had no effects on learning but enhanced consolidation, leading to improved retention. However, another study by this group showed that VNS impaired cognitive flexibility and creativity when administered prior to these tasks. Helmstaedter *et al.*, (2001) found reversible deterioration of figural but not verbal memory and accelerated decision times during VNS. But the differences in memory findings between this study and the

one by Clark *et al.*, (1999) may be due to when the stimulation was delivered during the task. The latest recent review on the cognitive side effects of VNS by Boon *et al.*, (2006) concluded that '*there is no evidence in favour of adverse cognitive effects of VNS, but most studies suggest that clear-cut positive effects cannot be expected either*'.

3.3.3 Psychosocial-related factors

There is a large body of evidence suggesting that people with epilepsy are at an increased risk of psychosocial problems (Jacoby, 2002). There is a higher prevalence of mood and psychiatric disorders (Dodrill & Batzel, 1986, Hermann *et al.*, 2000, Swinkels *et al.*, 2006), and a higher rate of suicide compared to the general population (Jones *et al.*, 2003). People with epilepsy are at increased risk of lowered self-esteem and low self-confidence (Watten & Watten, 1999), are more likely to be un or under-employed (Collings & Chappell, 1994, Jacoby *et al.*, 2005), are less likely to be married and experience greater social isolation (Baker *et al.*, 2005). They have to manage the psychological sequalae often associated with epilepsy. They are concerned about the unpredictability of their seizures, their seizure severity and seizure control, their medication and its social implications (Hayden *et al.*, 1992).

Psychological well-being in particular, mood disorders, can impact on cognitive functioning (e.g. Austin *et al.*, 1992, Paradiso *et al.*, 2001, Airaksinen *et al.*, 2005). Depression tends to reduce performance on tasks that require attentional resources or on timed tasks (Reitan & Wolfson, 1997). However, there are complex causal relationships between mood, particularly depression, and cognition. Cognitive problems may result from depressed mood; depression may result as a reaction to cognitive problems; or both may result from a shared pathophysiology (Helmstaedter *et al.*, 2004). Mula *et al.*, (2003) have suggested that cognitive problems such as mental slowing, concentration impairment and memory deficits may represent symptoms of depression.

In addition, epilepsy may impact on educational and occupational attainment. Children with epilepsy may have to take significant time out of their schooling, which may affect their educational outcome. This may also contribute to lowered expectations by parents, teachers, their peers and themselves and lead to a restriction of opportunity (Brown, 2006). Similarly,

Austin *et al.*, (1998) have shown that seizure severity is a high risk factor for academic underachievement and boys with severe epilepsy are most at risk. Academic achievement is important because it is highly correlated with intellectual functioning (Matarazzo & Herman, 1984) and is a marker of cerebral reserve, which may act as a protective factor to further cognitive decline (Jokeit & Ebner, 1999, Oyegbile *et al.*, 2004).

3.4 Summary

Throughout the centuries, epilepsy has been associated with cognitive dysfunction. People with epilepsy not only commonly report experiencing cognitive impairments, but also perform more poorly on objective cognitive measures. Both these objective and subjective complaints can disrupt day to day functioning (e.g. education, employment, family life, social relationships); affect psychological well-being (e.g. self-confidence, self-esteem, anxiety and depression) and impact on overall quality of life.

The causes of cognitive impairments in people with epilepsy are multifactorial. The main factors are the effects of the underlying lesion, epilepsy syndrome, seizure frequency, AED treatment and presence of a mood disorder. Due to the complex interactions between these factors, it can be difficult to untangle their specific effects. In a clinical setting, this makes it hard to determine the cause of cognitive dysfunction experienced by an individual patient. In addition, it means that many patients, for example, have to balance the risks and benefits of achieving seizure control with treatments that may be associated with cognitive side effects.

The majority of research has focused on the nature and cause of cognitive impairments in people with epilepsy, in particular, the cognitive side effects of antiepileptic drug treatment. However, there is a relatively recent interest in determining *when* these impairments develop and *how* they progress during the course of the disorder. A growing body of evidence has suggested that people with epilepsy may already be experiencing cognitive dysfunction at the time of diagnosis, before the impact of many of these factors (e.g. AED treatment, only a few seizures). But few prospective longitudinal studies have been conducted to investigate whether these impairments get worse over time. This will be discussed in the next chapter.

Chapter 4 Natural history of cognitive functioning

4.1 Overview of chapter

This chapter will review the literature on how cognitive functioning develops during the course of epilepsy. There will be a discussion of the studies that suggest that people with newly diagnosed epilepsy are already experiencing cognitive dysfunction at the time of diagnosis, before the start of antiepileptic drug treatment and following few seizures. The potential explanations for this will be explored. There will be a consideration of whether this cognitive dysfunction gets worse over time, drawing on evidence from cross-sectional and longitudinal studies. The gaps in our understanding of the cognitive functioning of people with newly diagnosed epilepsy will be highlighted and the aims and objectives of this thesis will be presented.

4.2 Cognitive impairments present at the time of diagnosis

4.2.1 Nature of cognitive impairments

As discussed in the previous chapter, epilepsy, seizure and treatment-related factors all contribute to the development of cognitive dysfunction in people with epilepsy. However, several previous studies have demonstrated that adults with epilepsy are already cognitively compromised at the time of diagnosis, before the onset of many of these factors (see Table 4.1). This dysfunction is evident across several cognitive domains with untreated patients with newly diagnosed epilepsy performing worse than healthy volunteers on measures of memory, sustained attention and concentration, mental flexibility and psychomotor functioning (Brodie *et al.*, 1987, Smith *et al.*, 1987, Kalviainen *et al.*, 1992, 2003, Helmstaedter *et al.*, 1993, 2005, Aikia *et al.*, 1995, 2001, Prevey *et al.*, 1998, Ogunrin *et al.*, 2000, Pulliainen *et al.*, 2000a).

However, it is important to note that not all patients with epilepsy experience these difficulties. A series of studies have shown that approximately 30-56% of patients experience mild memory and attention problems at epilepsy onset compared to healthy controls (Kalviainen *et*

al., 1992, Aikia *et al.*, 1995, 2001); although it is unclear why some people are more susceptible than others. Pulliainen *et al.*, (2000a) found that lower levels of education, older age, symptomatic epilepsy and more abnormal CT findings were associated with worse performance. Similarly, a published abstract by Helmstaedter *et al.*, (2005) found older age to be associated with poorer cognitive performance, in addition to later onset and a shorter duration of epilepsy. Type of seizure may also play a role. Aikia *et al.*, (2001) found moderate memory impairment to be associated with secondarily generalised seizures. Prevey *et al.*, (1998) showed that those with secondarily GTCS performed worse on concentration and mental flexibility tasks, although this was not supported by Pulliainen *et al.*, (2000a). Further work, therefore, is needed to identify those who may be already at risk of cognitive impairment.

Despite the accumulating evidence that people with epilepsy demonstrate cognitive impairment at the time of diagnosis, there are methodological shortfalls with some of these studies. Firstly, not all studies have assessed patients before AED medication, some have included those who have previously been treated or are presently undertreated (e.g. Brodie *et al.*, 1987, Smith *et al.*, 1987, Prevey *et al.*, 1998, Pulliainen *et al.*, 2000a, Ogunrin *et al.*, 2000, Aikia *et al.*, 2001). Not only may their prior exposure to AEDs negatively affect cognition but this suggests that they have a longer duration of epilepsy, which may also have had a negative impact through increased number of seizures. In fact, in the study by Smith *et al.*, (1987), the mean interval since first seizure and enrolment was 12.2 years. Secondly, some studies have small sample sizes, which may not have adequate power to detect differences between the groups (e.g. 14 patients in the study by Brodie *et al.*, 1987) and none reported power calculations. Finally, not all studies have undertaken comprehensive neuropsychological assessments. Some have focused only on verbal memory (e.g. Aikia *et al.*, 1995, 2001) and others on reaction time and psychomotor speed (e.g. Brodie *et al.*, 1987), missing other potentially affected cognitive domains.

Table 4.1: Studies investigating cognitive functioning in adults with newly diagnosed or untreated epilepsy

Study	PWE	Controls	Cognitive domains	Results
Brodie *et al* (1987)	14 untreated for at least previous 3 months. 66 chronic epilepsy with GTCS or CPS treated with AEDs	11 age-matched healthy subjects (hospital staff)	Reaction time, memory, psychomotor speed	Untreated patients < controls on choice RT, card sorting and memory. Treated patients < untreated patients and controls on same tasks and finger tapping
Smith *et al* (1987)	622 newly diagnosed, previously untreated or undertreated	75 equated for age, sex and education	General intellectual functioning, attention and concentration, mental flexibility, motor manipulation, emotional/mood states	PWE<controls on 11/14 measures, all except digit span, POMS Anger and Fatigue sub-scales
Kalviainen *et al* (1992)	74 newly diagnosed untreated and no known aetiology (46 single seizure, 28 several seizures)	39 healthy volunteers equated for age, sex, education and IQ	General intellectual functioning, verbal ability, verbal learning and memory, attention and flexibility of mental processing, simple psychomotor speed	No differences single vs. several seizures. No diff PWE vs. controls in IQ and verbal ability. PWE < controls attention and memory (part delayed recall, recognition and learning of the word list). 30% had subtle memory and attention dysfunction (>1SD)
Helmstaedter *et al* (1993)	16 newly diagnosed epilepsy either CPS or primary generalised seizures	19 age-matched healthy controls	Attention, visuoperceptual speed, verbal fluency, memory	PWE<controls in sustained attention, verbal learning ability and visual retention. Those with structural brain lesions sig poorer than those without lesions or controls

Aikia *et al* (1995)	56 newly diagnosed partial epilepsy and no other known brain pathology	48 healthy volunteers equated for age, sex, education and IQ	General intellectual functioning, verbal memory (list learning and story recall)	No diff PWE vs. controls on story recall, learning or immediate recall or recognition of a list. PWE < controls delayed recall of words and % retention. 52% PWE vs. 15% controls had mild (>1SD) impairments
Prevey *et al* (1998)	201 newly diagnosed or presently undertreated with symptomatic localisation-related epilepsy (either CPS or secondarily GTCS)	45 neurologically normal controls (non-medical hospital staff) equated for age and education	Motor speed and integration, verbal and visual memory, concentration and mental flexibility, general intellectual functioning, personality/emotional factors	Controls > PWE on 17/18 measures but not all reach stat sig. PWE sig worse on memory and motor speed/integration. Secondarily GTCS worse than CPS on concentration and mental flexibility tasks
Pulliainen *et al* (2000a)	59 newly diagnosed with partial or generalised seizures. 5 had been previously treated (AEDs withdrawn >5yrs ago)	26 healthy volunteers (hospital staff, city fire department, students, referrals from neurology outpatient clinic with no brain pathology) equated for age and sex	Motor function and co-ordination, attention, concentration and mental flexibility, learning and memory, general intellectual functioning	PWE < controls on 16/20 sig worse on motor co-ordination, mental flexibility and delayed visual memory tasks. But after Bonferroni correction, no sig diffs. No diffs partial vs. generalised. Lower education, higher age and symptomatic epilepsy with more abnormal CT findings associated with worse performance on tests of memory, concentration and mental flexibility
Ogunrin *et al* (2000)	60 newly diagnosed, previously untreated epilepsy from Nigeria	60 healthy volunteers matched in age, sex and education (recruited from outpatients/staff clinics)	Psychomotor speed/alertness, sustained attention and short-term verbal and visual memory	PWE sig < controls except for response bias on the vigilance test (both reacted impulsively)

Aikia *et al* (2001)	39 newly diagnosed, previously untreated patients with LTLE and 16 patients with chronic LTLE (duration >10yrs). Both groups cryptogenic and remote symptomatic seizures	46 healthy controls equated for age, sex, education and verbal IQ	Verbal intellectual ability and verbal memory (story recall and list learning)	Both newly diagnosed and chronic PWE < controls on list learning task. No diffs on story recall. Chronic LTLE most affected. 56% newly diagnosed have mild (>1SD) impairments on delayed recall vs. 17% controls and 36% vs. 4% moderate (>2SD). Moderate memory impairment not associated with aetiology or hippocampal volumes but secondarily generalised seizures
Kalviainen *et al* (2003)[T]	199 newly diagnosed focal epilepsy	47 healthy volunteers; 77 patients with a single seizure	General intellectual ability, verbal ability, verbal learning, memory and attention	PWE<controls and single seizure: VIQ, FSIQ object naming, verbal fluency and story recall. Both seizure groups<controls on recall of word list and letter cancellation
Helmstaedter *et al* (2005)[T]	31 untreated newly diagnosed with symptomatic or cryptogenic epilepsy	-	Intellectual functioning, attention, language and memory	17% had an IQ<85. 36-48% had impairments in attention, language and verbal and numeracy memory. Only 26% were unimpaired. Poor cognitive performance was related to later onset, older age and a shorter duration of epilepsy

PWE=people with epilepsy, GTCS=generalised tonic-clonic seizures, CPS=complex partial seizures, LTLE=left temporal lobe epilepsy, POMS=Profile of Mood State questionnaire RT= reaction time, SD=standard deviation

[T]These are published abstracts rather than peer-reviewed publications. The data from Kalviainen *et al* was presented at the annual meeting of the American Epilepsy Society in Boston, 2003. The data from Helmstaedter *et al* was presented at the 26th International Epilepsy Congress in Paris, 2005.

4.2.2 Causes of impairments

Despite these shortfalls, cognitive problems appear to be present at epilepsy onset, before the start of antiepileptic drug treatment and before the accumulating impact of recurrent seizures. Studies from the paediatric literature suggest that they may even antedate the first recognised seizure (e.g. Austin *et al.*, 2001, Berg *et al.*, 2005). The specific mechanisms causing these impairments are unclear but this implies that they may be the result of the epileptic process or reflect the underlying CNS dysfunction that has led to the epilepsy.

Role of the underlying aetiology and epilepsy syndrome

Epilepsy is a symptom of an underlying cerebral alteration, which may be the result of a wide variety of differing aetiologies (see section 2.2.6). As discussed in the previous chapter (see section on 'Epilepsy syndrome and underlying aetiology'), the underlying aetiology and structural pathology may affect cognitive functioning independently of the effects of seizures and treatment. In the study by Prevey *et al.*, (1998) approximately one third of their patients had sustained a head trauma and one third had cerebrovascular disease or another neurological disorder, which may account for their poorer cognitive performance. Similarly, a small study by Helmstaedter *et al.*, (1993) showed that newly diagnosed patients with a structural brain lesion performed significantly more poorly than those without a lesion. More abnormal CT findings and symptomatic epilepsy have been associated with worse memory, concentration and mental flexibility scores in another study of adults with newly diagnosed untreated epilepsy (Pulliainen *et al.*, 2000a).

Symptomatic/cryptogenic epilepsy was also found to be a risk factor for neuropsychological deficits in a study in children with a first recognised seizure (Fastenau *et al.*, 2009). A previous study by this group also found that 14% of children with new onset epilepsy had significant structural abnormalities that were judged to be related to their seizures, such as gliosis, hippocampal atrophy and cortical dysplasias. These abnormalities were associated with lower estimated IQ scores and lower language, processing speed, executive/constructional ability and verbal memory and learning scores. This association remained even after excluding those with general cognitive problems, defined as low intellectual functioning (IQ <70) (Byars

et al., 2007). The authors concluded that some of the variability in neuropsychological functioning in children with newly recognised seizures might be caused by the presence of an underlying structural brain abnormality. Consistent with this, another study in children demonstrated that those who had academic problems that predated the onset of epilepsy had reduced grey matter volumes in the left occipital and parietal lobes (Hermann *et al.*, 2006a).

Underlying brain abnormalities may explain some of these observed impairments. However, some studies have found cognitive and behavioural dysfunction at epilepsy onset in adults and children with no known aetiological factor for their epilepsy and are otherwise 'neurologically normal' (Kalviainen *et al.*, 1992, Aikia *et al.*, 1995, Oostrom *et al.*, 2003, Hermann *et al.*, 2006a, Berg *et al.*, 2005, Bhise *et al.*, 2009).

Role of epileptogenesis

The presence of impairments in those without neuroabnormalities implies that factors associated with the underlying epileptogenesis may play a role in cognitive dysfunction (Hermann *et al.*, 2006a, 2007b). Epileptogenesis refers to '*the alteration of a normal neural network into a hyperexcitable network in which recurrent, spontaneous seizures occur*' (Badawy *et al.*, 2009a, 2009b). Multiple mechanisms underlie epileptogenesis including abnormalities of neuronal structure and organisation from cortical malformations; ion channel dysfunction from single gene mutations and disturbances in network function (Badawy *et al.*, 2009a, 2009b). The mechanisms that lead to the development of epilepsy following a lesion or insult such as a tumour, head injury or stroke are still not understood. However, alterations are thought to occur, which may involve apoptosis, axonal sprouting, changes in excitatory and inhibitory neurotransmitters and network reorganisation. These alterations may result in the predisposition to have recurrent seizures (Badawy *et al.*, 2009a, 2009b). It is possible that these changes could contribute to the observed cognitive dysfunction. In support of this, a study by (Hermann *et al.*, 2006a) found no differences in the total cerebral or total lobar volumes in children with idiopathic new-onset epilepsy and healthy controls. However, the relationship between cognition and white matter volumes was different in the two groups, suggesting an altered functional relationship in children with epilepsy.

Role of psychological factors

As well as neurobiological factors, psychological factors may be an additional explanation for the impairments that exist at the time of diagnosis. As discussed in the previous chapter (section 3.3.3), there is a large body of evidence suggesting that people with epilepsy are at an increased risk of psychosocial problems (e.g. mood and psychiatric disorders, lower self-esteem, un or under-employment, fear of seizures, worry about stigma and social implications), which may impact on their cognitive functioning. In the previous chapter, these problems were discussed mainly in relation to those with more severe or established epilepsy. However, receiving a diagnosis of epilepsy also triggers a complex psychological adjustment process (Velissaris *et al.*, 2007).

Velissaris *et al.,* (2007) found that the initial reactionary period to a first diagnosed seizure was characterised by psychological (e.g. emotional reactions such as fear and shock, increased sense of vulnerability and diminished sense of self) and social issues (e.g. concerns about job security, being able to fulfil role in family and driving limitations) that are often experienced as a threat to a person's sense of control. Having a recent diagnosis of epilepsy has also been associated with problems such as decreased psychological well-being, fear of seizures and fear of stigma in employment (Chaplin *et al.*, 1992, Kemp *et al.*, 1999). As shown in the previous chapter, psychological well-being can impact on cognitive functioning; therefore, it is feasible that the psychological uncertainty associated with having a new diagnosis of epilepsy may impact on cognitive functioning at this time. In support of this argument, Oostrom *et al.,* (2003) found that the differences between children with new-onset epilepsy and sex and age matched classmates were not related to epilepsy characteristics but to the reaction of the child and parent to the diagnosis of epilepsy. However, despite finding more symptoms of depression, feelings of bewilderment and less vigour in adults with newly diagnosed epilepsy compared to healthy controls, Pulliainen *et al.*, (2000b) found that the deficits were not the result of depression or these negative mood states.

4.2.3 Summary

To summarise, several studies of children and adults have demonstrated that impairments are already present, certainly for some people with epilepsy, at the time of diagnosis, before the start of treatment and before the accumulating impact of recurrent seizures. The reasons for these impairments are unclear but are probably multifactorial reflecting the underlying brain dysfunction leading to the epilepsy; the effects of epileptogenesis and a psychological reaction to having a diagnosis of a chronic illness. However, another emerging question of interest is how these impairments develop over time. Do they get worse with increasing duration of epilepsy?

4.3 The development of impairments over time

As briefly mentioned in the previous chapter, a number of studies have been conducted to evaluate the relationship between duration of epilepsy and cognitive decline. In that section (see Section 3.3.1), the discussion centred on the cumulative effect of recurrent seizures on the brain. In this chapter the discussion, will focus on whether epilepsy represents a progressive dementia-type disorder. This review will draw on evidence from cross-sectional and longitudinal studies.

4.3.1 Findings from cross-sectional studies

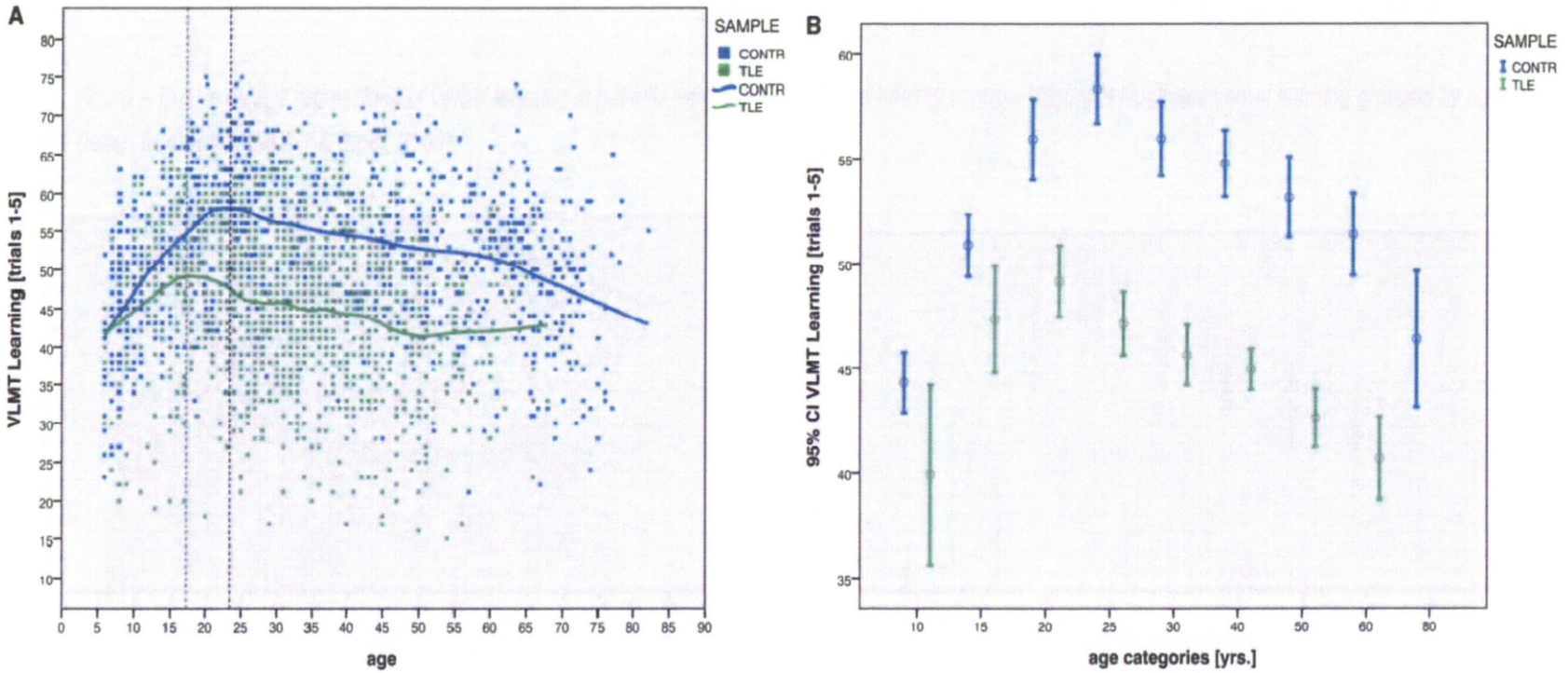
A number of cross-sectional studies have found that cognitive functioning declines with increasing duration of epilepsy (Jokeit & Ebner 1999, Jokeit *et al.*, 2000, Hermann *et al.*, 2002a, Oyegbile *et al.*, 2004, Kent *et al.*, 2006, Marques *et al.*, 2007). For example, Jokeit & Ebner (1999) showed that those with epilepsy duration of more than 30 years had worse Full Scale IQ scores than those with duration of less than 30 years. However, higher educational attainment, as an indicator of cerebral reserve, may modify this relationship and slow the rate of decline (Jokeit & Ebner, 1999, Oyegbile *et al.*, 2004).

Duration of epilepsy is a marker for increased number of seizures; exposure to AEDs; interictal epileptic brain activity; chronic and transient metabolic disturbances; risk of seizure-

related injuries and earlier age of onset, all of which may impact on cognition (Jokeit & Ebner, 1999, Oyegbile *et al.*, 2004). However, a number of studies have not found evidence of deterioration over time (e.g. Helmstaedter & Elger, 1999). In fact, Helmstaedter & Elger (1999, 2009) have argued that the association between duration and cognitive decline is confounded by the effects of ageing. They suggest that an alternative approach should be to compare the age regression measures of people with epilepsy with those of healthy controls (see Figure 4.1). Their recently published data from 1156 patients with refractory TLE and 1000 healthy controls (aged between 6-80yrs) suggest that the memory functioning of patients with epilepsy runs parallel to that of healthy volunteers throughout the lifespan but their memory performance is at a lower level (see Figure A). The authors say that these results imply that there is a neurodevelopmental hindrance in chronic TLE, which affects learning and memory functioning, but this is then followed by normal physiological ageing and not progressive accelerated decline (see Figure B) (Helmstaedter & Elger, 2009). Similarly, Hermann *et al.*, (2002a, 2002b) propose that TLE, particularly of childhood-onset, is also associated with a generalised adverse neurodevelopmental impact on brain structure and function. But they suggest that this represents an early acquired vulnerability, which reduces cerebral reserve, and then places patients at risk for progressive cognitive decline.

The findings of cross-sectional studies have been mixed, which impairs the ability to draw firm conclusions. Additionally, despite cross-sectional studies being useful to look at the relationships between cognition and long duration of epilepsy in large samples of patients (Jokeit & Ebner, 2002, Helmstaedter, 2002, Hermann *et al.*, 2008a), they have several limitations. For example, cause and effect cannot be determined and there may be undetected cohort bias effects, such as improvement in diagnosis or new antiepileptic drugs (Jokeit & Ebner, 1999, Helmstaedter, 2002). Therefore, a more appropriate approach to investigate changes in cognition is to follow the same group of individuals prospectively in longitudinal studies (Seidenberg *et al.*, 2007).

Figure 4.1: Figure A illustrates age regressions of verbal learning in patients with chronic TLE and healthy controls. Figure B illustrates verbal learning grouped by age increments (taken from Helmstaedter & Elger, 2009)



4.3.2 Findings from longitudinal studies

Comparatively, there have been few longitudinal studies conducted in adults with epilepsy and many have small sample sizes. This probably reflects the financial and time resources needed to conduct studies of this type. Two recent reviews (Dodrill, 2004, Seidenberg *et al.*, 2007) have identified all the published longitudinal studies addressing this issue. Dodrill (2004) found 13 studies in adults published since 1942 and Seidenberg *et al.*, (2007) found six studies published between 2004 and 2007. For the purposes of this review, two additional studies have been identified that were published during this time frame (Aikia *et al.*, 2001, Huang *et al.*, 2005). Since the latest review in 2007, no further longitudinal studies have been identified. However, there has been a re-analysis of the study by Andersson-Roswall *et al.*, (2004) exploring the reasons for decline in verbal memory (Andersson-Roswall *et al.*, 2007) and Hermann *et al.*, (2007a) have applied their three cognitive phenotypes to the patients studied in Hermann *et al.*, (2006b). Table 4.2 summarises all the longitudinal studies addressing the issue of cognitive progression in adults with epilepsy.

Table 4.2: Longitudinal studies of cognitive functioning (adapted from Dodrill, 2004 and Seidenberg et al., 2007)

Study	PWE	Controls	Test-retest interval	Cognitive domains	Results
Arieff & Yacorzynski (1942)	27 patients with symptomatic epilepsy	-	1-10 yrs (each individual tested 2-5 times)	General intellectual functioning	Sig decline in IQ (mean 6 points) between first and last test. 22% patients sig increased and 37% patients sig decreased
Rodin (1968)	56 adolescents and adults	-	Mean 7 yrs (at least 5yrs)	General intellectual functioning	60% of those who had been seizure free for at least 2 yrs increased in FSIQ. 25% of those who had improved seizure freq but were not seizure free increased FSIQ and only 15% of those whose seizure frequency was same or worse increased FSIQ. Changes in seizure frequency correlated with FSIQ.
Seidenberg *et al* (1981)	47 adults: 22 seizures improved (SI) and 25 seizures unimproved (SU)	-	SI group: Mean 18.6±7.3mths SU group: 19.4± 4.6mths	General intellectual functioning	SI group sig improved in VIQ, PIQ and FSIQ. SU group sig improved on PIQ.
Dodrill & Wilensky (1990)	9 adults with status epilepticus	9 matched adults with no status	5 yrs (± 6 mths)	General intellectual functioning, mental flexibility, verbal and visual memory, psychomotor speed, language, visuo-perceptual functioning	Non-status group improved on FSIQ and trend for VIQ

Kalska (1991)	69 adults who took part in a 4 week vocational rehabilitation programme	-	Mean 9.4±0.98yrs, range 6-11yrs	General intellectual functioning, memory, cognitive flexibility, motor function, personality, health locus of control	Majority of measures either unchanged or improved across group. 64-89% of PWE unchanged on various tests.
Dodrill & Wilensky (1992)	33 adults with partial seizures who did not change medication	-	5 yrs (± 6 mths)	General intellectual functioning, mental flexibility, verbal and visual memory, psychomotor speed, language, visuo-perceptual functioning	Few sig changes in mental abilities and no losses
Selwa *et al* (1994)	28 adults with TLE	-	2.36 ± 1.87 yrs, range 1-8 yrs.	General intellectual functioning, memory	No mean deterioration of intellectual or memory functioning. Stat sig improvement in FSIQ (mean 3 point) and PIQ (mean 4 point) but not clinically sig.
Holmes *et al* (1998)	35 adults with refractory complex partial epilepsy	-	10 yrs	General intellectual functioning, mental flexibility, verbal and visual memory, psychomotor speed, language, visuo-perceptual functioning	Generally no change in intellectual performance but stat sig increase in PIQ (mean 3 points). No change in neuropsychological functioning but few subtle losses on some measures (particularly, speed of response and visual-spatial relations).

Aikia *et al* (1999a)[5]	58 untreated patients with newly diagnosed partial epilepsy	-	5 yrs	General intellectual functioning, verbal ability, verbal learning and memory, attention and flexibility of mental processing	No significant decline. Improvements in several neuropsychological tests due to normal practice effect
Helmstaedter *et al* (2000)	47 patients with TLE	-	56 ± 26 mths, range 2-10 yrs	General intellectual functioning and memory	Generally stable but declines in visual memory. 37% sig declined in memory functioning and 5-10% improved
Aikia *et al* (2001)	20 with newly diagnosed TLE	-	5 yrs	Verbal intellectual ability and verbal memory	No deterioration in verbal memory. Improvements in delayed verbal recall.
Bjørnæs *et al* (2001)	17 adults with refractory epilepsy who were epilepsy surgery candidates	-	6 ± 4.8 yrs	General intellectual functioning	Sig increases in PIQ (mean 7.9 points) and FSIQ (mean 6.4 points).
Dodrill (2002)	35 adults with partial epilepsy with or without secondary generalisation	35 normal controls matched for age, sex and education	10 yrs (± 6 mths)	General intellectual functioning, mental flexibility, verbal and visual memory, psychomotor speed, language, visuo-perceptual functioning	Control group sig improved on mental flexibility and PIQ (7 points). PWE improved on PIQ (3 points). Both groups declined in visual memory. No relationship between no of partial seizures and cog changes. GTCS correlated with changes on 2 measures (FSIQ and Trail making).

[5] This is a published abstract rather than a peer-reviewed publication. The data was presented at the 23rd International Epilepsy Congress in Prague, 1999.

Helmstaedter *et al* (2003)	102 adult patients with chronic TLE	-	Median 52 mths, range 2-10 yrs	Memory, attention and verbal fluency, general intelligence, mood and QOL	50% had sig memory decline. No sig changes in non-memory functions.
Andersson-Roswall *et al* (2004)	36 patients with refractory localisation-related partial epilepsy	25 healthy controls (friends, colleagues and spouses of PWE)	PWE: median 4.8yrs, range 1.4-9.3yrs. Controls: 3.1yrs, range 2.8-3.3 yrs.	General intellectual functioning, learning and memory	Controls sig improved on FSIQ (avg 3 points) and PIQ (avg 6 points). PWE sig declined in verbal memory (delayed recall). PIQ change scores differed from controls. No change in general intellectual functioning or visual memory.
Pai & Tsai (2005)	64 patients recruited from outpatient clinic (31 high education and 33 low education)	-	12 months	Memory, attention, mental manipulation, orientation, abstract thinking, language, drawing, verbal fluency.	Those with high education had deterioration in mental manipulation. Those with low education had improvements in verbal memory but deteriorations in attention.
Huang *et al* (2005)	100 patients with cryptogenic epilepsy (64 normal and 36 abnormal cognitive scores at initial testing)	-	3 yrs, range 2-5 yrs	Memory, attention, mental manipulation, orientation, abstract thinking, language, drawing, verbal fluency.	Those with abnormal scores at initial testing had sig improvement in overall cognition scores and short term memory and semantic fluency. Normal group had no sig change.
Thompson & Duncan (2005)	136 patients with severe intractable epilepsy	-	Median 13 yrs, range 10-27 yrs	Intellectual level, memory, language, executive skills	Sig cognitive decline across all domains. Frequency of GTCS strongest predictor of decline.

Hermann *et al* (2006b)	46 patients with chronic TLE	65 healthy controls matched in age, sex and education (friend or relative of PWE)	4 yrs	Intelligence, language, visuoperceptual/spatial skills, memory, executive functions, speed psychomotor processing and fine motor dexterity	PWE had different cognitive trajectories. Controls improved 9/16 measures. PWE improved on 1/16. Adverse cognitive outcomes in 20-25%, particularly memory, psychomotor speed. Decline associated with baseline quantitative MRI abnormalities, lower baseline intellectual capacity, longer duration of epilepsy and older age.
Piazzini *et al* (2006)	50 patients with TLE	50 controls (selected from university list of research volunteers)	5 yrs	Non-verbal intelligence, attention and psychomotor speed, language fluency, language oral comprehension, verbal and visual memory	PWE sig decline in attention and psychomotor speed. Decline on these measures was related to duration, age at onset, history of GTCS and low education level
Griffith *et al* (2007)	17 older adults with epilepsy	17 healthy older adults matched for age, sex and education (university list of volunteers)	34±5.87 mths	Overall cognitive function, verbal memory, verbal fluency, confrontation naming, executive control and self-reported mood	Cognition remained stable at FU but declines in executive control.

PWE=people with epilepsy, FSIQ=Full Scale IQ, VIQ=Verbal IQ, PIQ=Performance IQ, TLE=temporal lobe epilepsy, GTCS=generalised tonic-clonic seizures, QOL=Quality of Life, MRI=magnetic resonance imaging, FU=follow-up

Similar to the results from the cross-sectional studies, the results from these longitudinal studies are mixed. Some have suggested that as a group, people with epilepsy decline in areas of functioning, particularly in memory, attention, executive control, speed of response and visual-spatial relations (Arieff & Yacorzynski, 1942, Holmes *et al.*, 1998, Helmstaedter *et al.*, 2000, 2003, Andersson-Roswall *et al.*, 2004, Thompson & Duncan, 2005, Hermann *et al.*, 2006b, Piazzini *et al.*, 2006, Griffith *et al.*, 2007). However, there is variability in cognitive outcome. For example, Helmstaedter *et al.*, (2000) identified 37% of patients with temporal lobe epilepsy who declined in memory functioning; Arieff & Yacorzynski (1942) also identified 37% who significantly decreased in intellectual functioning and Hermann *et al.*, (2006b) identified 20-25% who had adverse cognitive outcomes.

In a related study, Hermann *et al.*, (2007a) found that the three cognitive phenotypes they identified in patients with chronic TLE (described in section 3.2.1) not only had different cognitive profiles but also had a different cognitive course over a period of four years. Those who exhibited most impairments (the memory, executive and speed impaired group) had a poorer cognitive course than the other two groups. The factors that have been associated with cognitive decline include seizure frequency, in particular, frequency of GTCS; baseline quantitative MRI abnormalities; lower baseline intellectual capacity; longer duration of epilepsy and older age (Rodin, 1968, Seidenberg *et al.*, 1981, Dodrill, 2002, Thompson & Duncan, 2005, Hermann *et al.*, 2006b, Piazzini *et al.*, 2006). As found in the cross-sectional studies, cognitive decline may also be modified by cerebral reserve (Huang *et al.*, 2005, Pai & Tsai, 2005).

In contrast, several studies have suggested either improvements or generally stable functioning over time (Seidenberg *et al.*, 1981, Kalska, 1991, Dodrill & Wilensky, 1992, Selwa *et al.*, 1994, Holmes *et al.*, 1998, Aikia *et al.*, 1999a, 2001, Bjørnæs *et al.*, 2001, Dodrill, 2002, Griffith *et al.*, 2007). However, the majority of these did not include a comparison control group to compare with 'normal' change, which will be discussed in more detail below.

Methodological shortfalls of previous longitudinal studies

Despite using more appropriate longitudinal designs, there are methodological shortcomings with many of these studies, which may explain the variability in findings. These have been discussed by Seidenberg *et al.,* (2007) and Hermann *et al.*, (2008a) and are summarised in Table 4.3.

Table 4.3: Methodological shortfalls of longitudinal studies

Methodological shortfalls	Why is this important?
No comparison control group	• Unable to make conclusions with regards to 'normal' performance
Varied test-retest intervals both *between* and *within* studies	• Makes comparing studies difficult • May not be long enough intervals to detect cognitive changes
Small samples sizes	• May not have adequate power to detect change
Inconsistency in cognitive domains studied and choice of neuropsychological tests	• Makes comparing studies difficult • Some studies only focused on intellectual functioning ignoring cognitive domains (e.g. memory) which are known to be vulnerable to the effects of epilepsy
Focus on those with severe, chronic, intractable epilepsy	• May not be generalisable to those with new onset or well-controlled epilepsy

Firstly, until recently, very few studies employed a comparison control group. In fact, only five studies have used a control group and these have arrived at different conclusions. These controlled studies have found that the patients with epilepsy have a different cognitive trajectory to healthy volunteers, which is characterised by a lack of a practice effect (Dodrill, 2002, Andersson-Roswall *et al.,* 2004, Hermann *et al.*, 2006b, Piazzini *et al.,* 2006, Griffith *et al.,* 2007). For example, Hermann *et al.,* (2006b) found improvements by controls on nine of 16 cognitive measures but improvements by the epilepsy group on only one of the 16 measures. Similarly, Andersson-Roswall *et al.*, (2004) found that the Performance IQ scores of people with epilepsy did not change whilst the healthy controls increased by six points. A lack of a practice effect may reflect a deficit or impaired capacity for learning from prior exposure to the initial testing experience (Andersson-Roswall *et al.,* 2004, Seidenberg *et al.,* 2007). The use of a comparison control group means that the performance of people with epilepsy can be evaluated against the 'normal' performance of healthy volunteers to identify

'abnormal' functioning over time, which may be more apparent than abject deterioration (Seidenberg *et al.,* 2007, Hermann *et al.,* 2008a).

Secondly, the studies have used varied test-retest intervals. These have largely ranged between one and ten years, although Thompson & Duncan (2005) included an individual with a test-retest interval of 27 years in their retrospective study. The differing intervals make comparisons across studies difficult and some may not be long enough to detect clinically significant cognitive changes. However, Seidenberg *et al.,* (2007) suggested that a *'3-4 year interval is likely to be sufficient to detect evidence of significant cognitive change in adults with epilepsy and that longer retest intervals may be associated with greater cognitive progression'.* Additionally, small sample sizes also mean that the studies may not have adequate power to detect clinically significant change. The median sample size in the longitudinal studies reported above was 46.5 [Interquartile Range (IQR) 31.75-59.50] with the smallest study by Griffith *et al.,* (2007) only involving 17 patients.

Thirdly, the studies have investigated different cognitive domains and used different neuropsychological assessments. Earlier studies focused solely on intellectual functioning (e.g. Arieff & Yacorzynski, 1942, Rodin, 1968, Seidenberg *et al.,* 1981), which probably reflected the fact that epilepsy was historically associated with intellectual deterioration (e.g. Gowers, 1885, Lesser *et al.*, 1986). However, this ignores cognitive domains that are known to be vulnerable to the effects of epilepsy and its treatment, in particular memory functioning. While later studies have moved towards examining changes in other key neuropsychological areas, the domains and tests selected are not consistent across studies. Table 4.4 highlights the inconsistency of test selection in the assessment of memory alone.

Seventeen of the 21 longitudinal studies included an assessment of memory functioning. Eighteen tests were identified as being used, of which the most frequently employed was the Logical Memory subtest from the Wechsler Memory Scale (WMS), which was used in seven of the studies (Dodrill & Wilensky, 1990, 1992, Selwa *et al.,* 1994, Holmes *et al.,* 1998, Aikia *et al.,* 2001, Dodrill, 2002, Griffith *et al.,* 2007). Some form of list learning task was employed in five of the studies (Helmstaedter *et al.,* 2000, 2003, Aikia *et al.,* 2001, Andersson-Roswall *et al.,* 2004, Thompson & Duncan, 2005). However, different versions were often used, although

this was mainly due to language modifications (e.g. translations into German and Swedish). Nine tests were only used once. The lack of uniformity and standardisation in the choice of neuropsychological test batteries makes comparing results across studies and drawing firm conclusions difficult.

Table 4.4: Heterogeneity of neuropsychological tests used in longitudinal studies in people with epilepsy[6]

Memory assessment	Frequency of use
Wechsler Memory Scale Logical Memory	7
Wechsler Memory Scale Visual Reproduction	5
Seashore Tonal Memory	4
Tactual Performance Test	4
Cognitive Ability Screening Instrument	2
DCS-R (German figural design list-learning test)	2
Rey-Osterrieth Complex Figure Memory Test	2
VLMT (German equivalent of the Rey Auditory Verbal Learning Test)	2
Wechsler Memory Scale -III or earlier versions (all subtests)	2
Benton Visual Retention Test	1
Claeson-Dahl Learning and Retention Test (list learning task)	1
List learning (modified from the Rey Auditory Verbal Learning Test)	1
List learning from the Adult Memory and Information Processing Battery	1
Wechsler Memory Scale Paired Associates	1
Cronholm-Molander Memory Test (paired associates task)	1
Paired associate words test (version not specified)	1
Digit span (version not specified)	1
Story test (version not specified)	1

Finally, the majority of studies have largely included those with severe, chronic, intractable epilepsy often of long duration [e.g. mean duration of 14.8 years in Bjørnæs *et al.*, (2001); 17 years in Helmstaedter *et al.*, (2003) and 20 years in Holmes *et al.*, (1998)]. Only two studies by Aikia and colleagues (1999a, 2001) have included those with newly diagnosed epilepsy. The study by Aikia *et al.*, (1999a) is a published abstract from a paper that was presented at a conference. They followed-up 58 patients with newly diagnosed partial epilepsy over five years and found no significant declines across a comprehensive neuropsychological test battery. However, in the study by Aikia *et al.*, (2001) they presented preliminary data that only

[6] The specific neuropsychological tests used in Aikia *et al.*, (1999) were not reported in their published abstract so while this study included an assessment of memory functioning, this study is not included in the table.

focused on verbal intellectual and verbal memory functioning in 20 patients with newly diagnosed TLE. They also found no significant declines after five years in verbal memory. But neither of these studies reported on a control group, so no conclusions can be made about whether this stable performance represents 'normal' functioning. The lack of studies in this patient group means our understanding and knowledge of the additional impact of treatment and seizures on the pre-existing impairments discussed earlier in this chapter is limited.

4.3.3 Summary

In summary, neither cross-sectional nor longitudinal studies have been able to provide a definitive answer as to whether cognitive functioning declines over time in people with epilepsy. Cross-sectional designs are associated with limitations in answering this type of question, although they are able to provide data from a large number of patients over a long duration of epilepsy. A better approach is a longitudinal design, however, there have only been 21 longitudinal studies published since 1942. These have also found mixed results, which probably reflect their differing methodologies. The studies have varied in their test-retest intervals, the cognitive domains studied and neuropsychological tests used and the type of patients assessed. A review of this area has highlighted that there is a gap in the literature, relating to the cognitive functioning of adults with newly diagnosed epilepsy.

4.4 Gaps in the literature

In comparison to those with chronic, long-standing epilepsy very little is known about the cognitive functioning of adults with newly diagnosed epilepsy. A few studies have found that people with epilepsy have cognitive impairments at the time of diagnosis but these studies have used different methodologies which make determining the mechanisms underlying the cognitive impairments present at baseline unclear (e.g. some patients have previously been treated; some include those with known pathologies and few measure current mood states). No previous study has only included those who are previously untreated with no known pathology or aetiology; evaluated a wide variety of cognitive domains, and measured current mood state in comparison to a matched healthy control group.

The issue of cognitive decline in people with epilepsy is still uncertain. It is even less certain for those who develop epilepsy in adulthood. Only one published study (Aikia *et al.*, 2001) and one published abstract (Aikia *et al.*, 1999a) have investigated cognitive changes in adults who are newly diagnosed. However, these had a relatively small sample size, did not employ a control group and the study by Aikia *et al.*, (2001) only evaluated verbal memory performance, as part of their preliminary data. In addition, recent studies, particularly by Hermann *et al.*, (2007a), have suggested that people with epilepsy have different cognitive trajectories compared with healthy controls. No previous study has investigated whether these cognitive trajectories are evident in those with newly diagnosed epilepsy. Therefore, there is a need for a prospective, longitudinal, controlled study charting cognitive functioning and mood in people with epilepsy over a period of years from the time of diagnosis.

4.5 Aims and objectives of the thesis

4.5.1 Aims

The overall aim of this thesis is to gain a greater understanding of the natural history of cognitive functioning in people with newly diagnosed epilepsy.

4.5.2 Objectives

- To compare the cognitive profile of healthy volunteers with newly diagnosed untreated people with newly diagnosed epilepsy and no known cerebral pathology, before the administration of antiepileptic drug medication.
- To compare the cognitive trajectories of people with newly diagnosed epilepsy and healthy volunteers over the first 12 months after starting AED treatment.
- To document the longer term effects of epilepsy and its treatment on cognitive functioning in people with newly diagnosed epilepsy.

4.6 Summary

There has been extensive research investigating the nature and cause of cognitive problems experienced by people with epilepsy. An area of increasing interest is the timing of these impairments in the course of the disease and whether these problems get worse over time. Several studies have suggested that patients with newly diagnosed epilepsy are already experiencing cognitive dysfunction at the time of diagnosis. However, only two studies have followed these patients over the course of their epilepsy. The results of previous longitudinal and cross-sectional studies investigating cognitive changes in patients with severe, chronic or intractable epilepsy have been mixed. Some have suggested stable functioning over time, while others have suggested deteriorations with increasing duration of epilepsy. There are methodological differences between these studies, which may account for the mixed findings. There is a gap in our understanding of the natural history of cognitive functioning in people with newly diagnosed epilepsy. This has led to the development of the aims and objectives of this thesis. The next chapter will discuss the research methods used to investigate these aims.

Chapter 5 Design and methods

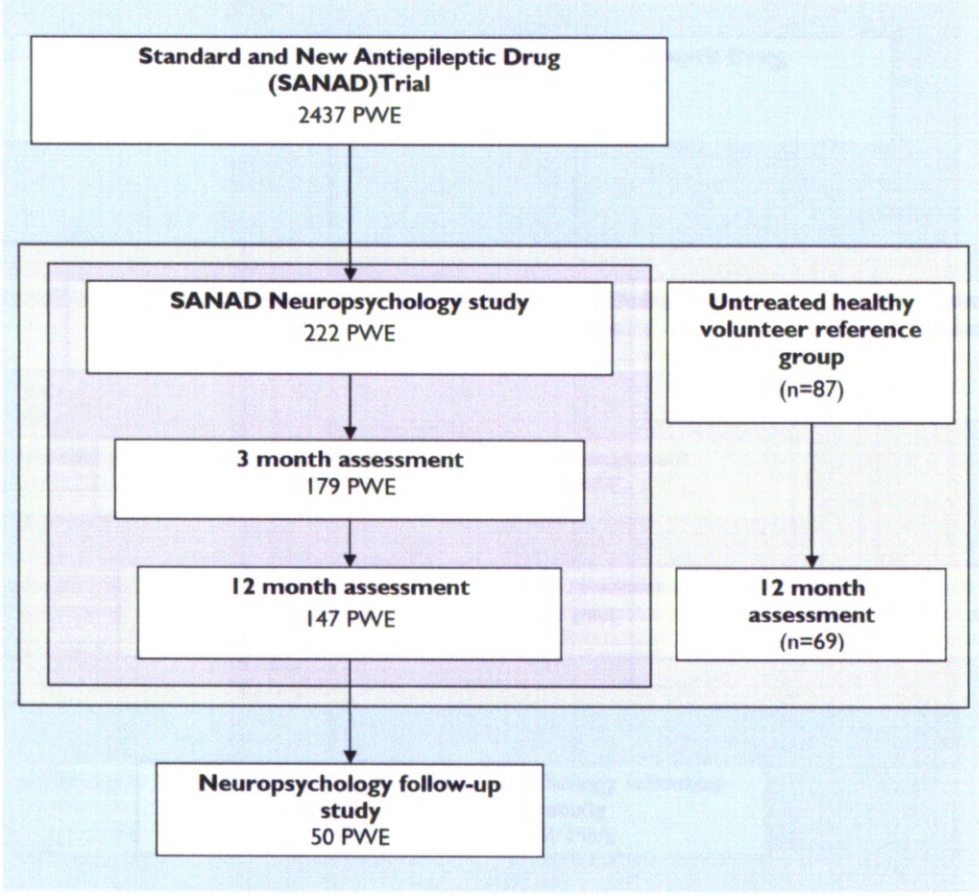
5.1 Overview of the chapter

This chapter will outline the research methods used to investigate the natural history of cognitive functioning in people with newly diagnosed epilepsy. As illustrated in Figure 5.1, this research took place in the context of the SANAD trial (Marson *et al.*, 2007a, 2007b). The background to this trial and its procedures will be provided. From the SANAD trial, untreated patients with newly diagnosed epilepsy were invited to take part in the SANAD Neuropsychology study. The neuropsychological profile of these patients was then compared to the neuropsychological profile of healthy volunteers recruited from the general population, who were also assessed at baseline and 12 months. The background to this study, participants and procedure will be described. Patients with epilepsy who had completed assessments as part of the SANAD Neuropsychology study were invited to take part in a neuropsychology follow-up study. This was to investigate the longer term impact of epilepsy and its treatment on cognitive functioning. The design, participants and procedure of this study will be reported. The statistical analysis plan for the three results chapters will be outlined.

5.2 The SANAD trial

A full description of the methodology for the SANAD trial is contained in the publications by Marson *et al.*, (2007a, 2007b) and the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) report by Marson *et al.* (2007c). However, for brevity, only a brief summary of the trial's aims, design and methods will be presented here, to place the neuropsychological research in context.

Figure 5.1: Flowchart explaining the relationship between the Neuropsychology studies in this thesis and the SANAD trial



5.2.1 Aim

SANAD aimed to compare the clinical and cost effectiveness of standard drug treatments (carbamazepine or valproate) with comparator new drugs (gabapentin, lamotrigine, oxcarbazepine, topiramate) in people with epilepsy.

5.2.2 Design

The SANAD study was a pragmatic, randomised, unblinded, parallel group clinical trial comprising two arms. One arm (Arm A) comparing new antiepileptic drugs (gabapentin,

lamotrigine, oxcarbazepine and topiramate) with carbamazepine, which was widely accepted as the drug of first choice for patients with partial-onset seizures. The other arm (Arm B) comparing new antiepileptic drugs (lamotrigine and topiramate) with valproate (see Figure 5.2), which was widely accepted as the drug of first choice for patients with generalised onset seizures and was recommended for those whose seizures are difficult to classify.

5.2.3 Participants

The SANAD trial recruited patients with epilepsy from hospital outpatient clinics at 90 hospital centres in the United Kingdom. The first patient was randomised in January 1999 and randomisation continued until August 2004. A total of 1721 patients were randomised to Arm A and 716 patients to Arm B. Arm A recruited 88% of patients with symptomatic or cryptogenic partial epilepsy and 10% with unclassified epilepsy. Arm B recruited 63% of patients with idiopathic generalised epilepsy and 25% with unclassified epilepsy.

Inclusion/exclusion criteria

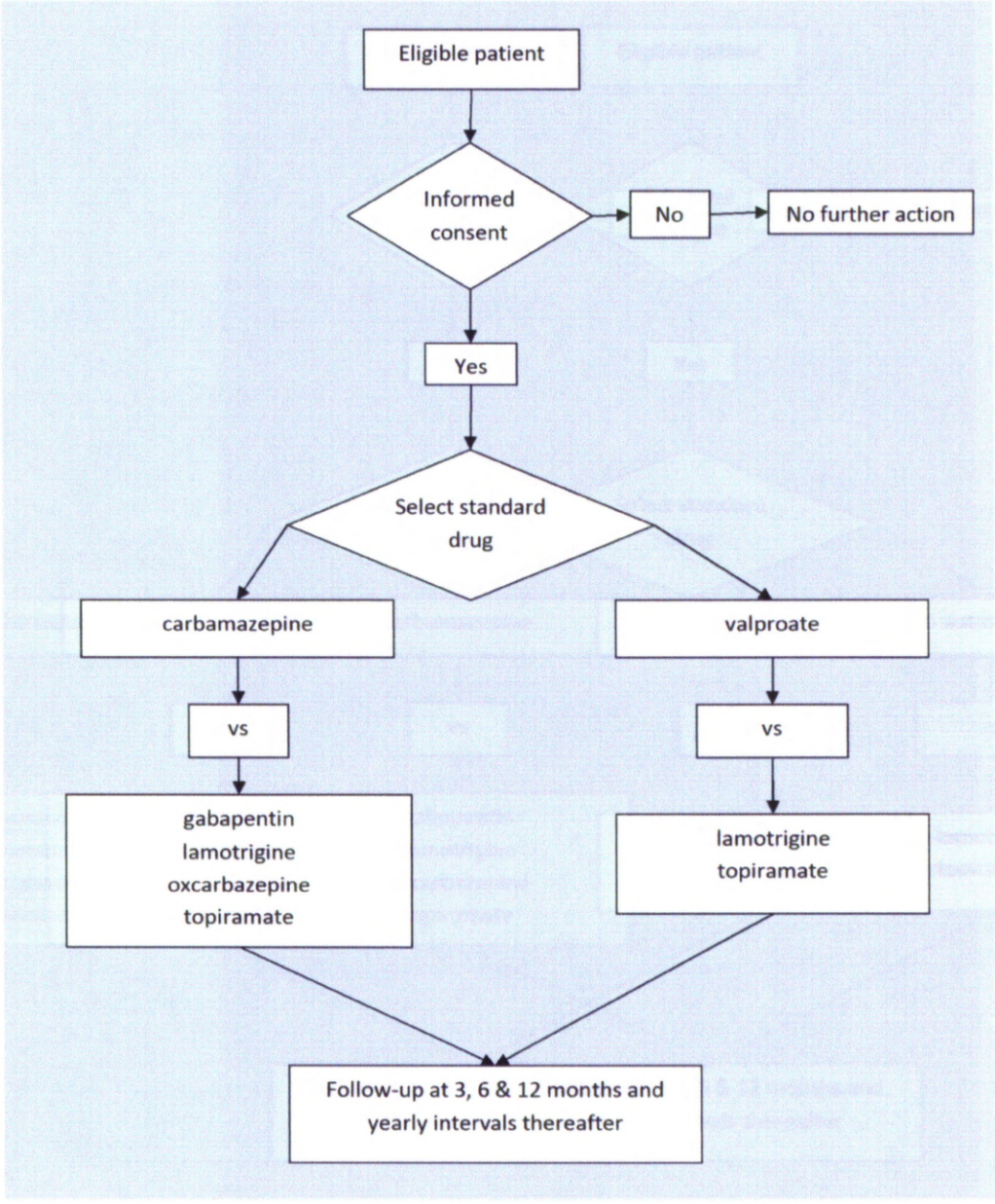
Patients were recruited into SANAD if they satisfied the inclusion criteria of a history of two or more clinically definite unprovoked epileptic seizures in the previous year; if treatment with a single AED represented the best therapeutic option and if they had given informed consent. This meant that SANAD could comprise patients with newly diagnosed epilepsy; patients who had failed treatment with previous monotherapy (as long as drug failure did not include one of the drugs involved in SANAD) and patients in remission of epilepsy, who had relapsed following the withdrawal of their treatment.

Patients were excluded if the clinician or patient felt that treatment was contraindicated; all their seizures had been acute symptomatic seizures including febrile seizures; they were aged four years or younger or there was a history of progressive neurological disease.

5.2.4 Procedure

Patients with epilepsy were randomised into one of two arms depending on which of the two standard treatments (carbamazepine or valproate) the clinician thought was most appropriate for the patient.

Figure 5.2: SANAD randomisation procedure (taken from the SANAD Participants Manual)



If the clinician thought carbamazepine was the most appropriate, then the patient was randomised to Arm A and was then randomly allocated to either the standard drug (carbamazepine) or the new drugs (gabapentin, lamotrigine, oxcarbazpine, topiramate). Randomisation was in the ratio of 1:1:1:1:1. However, oxcarbazepine was only included in the randomisation after 1 June 2001, therefore, fewer patients were randomised to this drug. If the clinician thought valproate was the most appropriate drug, then the patient was randomised to Arm B and was then randomly allocated to either the standard drug (valproate) or the new drugs (lamotrigine, topiramate). Randomisation was in the ratio of 1:1:1 (see Figure 5.2).

Randomisation was undertaken by telephoning the Randomisation Centre at the Centre for Cancer Epidemiology, Manchester. Randomisation was balanced across a number of factors (centre, sex, previous epilepsy history) to produce comparable groups.

While the choice of drug was randomised, the drug dosage and drug preparation were those used by the clinician in their everyday practice. During the study, the clinician and patient could agree that withdrawal of the randomised drug was necessary because of intolerable side effects; lack of efficacy or remission or that an additional AED drug should be added because of lack of efficacy. The choice of additional or alternative drugs was determined by the clinician according to their view of optimal clinical practice.

Demographic and clinical information was collected at baseline by the recruiting clinician. The information recorded at baseline is shown in Table 5.1. Patients were then followed-up by the recruiting clinician at three, six and 12 months and at successive yearly intervals after that. Patients were followed up more frequently, if required, as part of their clinical management. At every follow-up visit, occurrence of seizures; experience of adverse events; number of hospital admissions and AED treatment was recorded. Attempts were made to follow-up all patients to, at the latest 31 August 2005, although some follow-up data was collected up until 31 January 2006. The demographic and clinical data over the first year was made available to the author for analysis in this thesis.

Table 5.1: Information recorded at entry into SANAD

Information recorded	Definition
Demographics	• Sex and age
History of learning disability	• A history of at least one of the following: o additional educational support in > 2 subjects o a statement of educational needs o attends (or attended) a special school
Neurological deficit	• Localising neurological signs resulting in functional impairment
History of previous or current neurological disorder (e.g. stroke/cerebrovascular, intracranial surgery, head injury, meningitis/encephalitis, other)	• Head injury was defined as post-traumatic amnesia >24 hours or depressed skull fracture
History of seizures: febrile seizures; acute symptomatic seizures	• **Febrile seizures** were defined as those usually occurring between 3 months and 6 years. They were associated with fever but no evidence of an intracranial infection or a defined cause. • **Acute symptomatic seizures** were defined as those that occurred in the presence of an encephalopathy due to metabolic disturbance or drugs, or due to an acute cerebral illness.
History of epilepsy in a first-degree family member	• History of epilepsy in a first-degree family member
Number and type of seizures (including dates of first and most recent of each type)	• Classified according to the ILAE (1981) classifications
Epilepsy syndrome	• Classified according to the ILAE (1989) classifications
Results of EEG or brain imaging (CT/MRI) at time of randomisation	• Undertaken within 3 months of randomisation

5.2.5 Outcome measures

The two primary clinical outcome measures in the SANAD trial were the time from randomisation to treatment failure, and the time from randomisation to the achievement of a one year period of remission of seizures. Secondary clinical outcome measures were the time from randomisation to a first seizure; the time to achieve a two-year remission, and the incidence of clinically important adverse events and side effects emerging after

randomisation. Data was also collected on quality of life and health economic outcomes but these have been reported elsewhere.

5.3 SANAD Neuropsychology study

The SANAD Neuropsychology study was designed by Professor Gus A Baker (see Appendix A). Its main aim was to compare the cognitive side effects of standard and new AEDs in people with newly diagnosed epilepsy after three and 12 months of treatment. Unfortunately, this aim could not be met due to the small numbers of patients who were recruited into each drug group. However, for the purposes of this thesis, the SANAD Neuropsychology study provided a *unique* opportunity to investigate the natural history of cognitive functioning in a group of previously untreated patients with newly diagnosed epilepsy. Therefore, this study was used to investigate two of the objectives of this thesis:

- To compare the cognitive profile of healthy volunteers with people with newly diagnosed epilepsy and no known cerebral pathology, before the administration of antiepileptic medication.
- To compare the cognitive trajectories of people with newly diagnosed epilepsy and healthy volunteers over the first 12 months after starting treatment.

To meet these objectives, a healthy volunteer reference group was recruited and assessed from the general population separate to the SANAD Neuropsychology study. The design, participants and procedure for the SANAD Neuropsychology study, as well as the procedure for recruiting the healthy volunteer group, will be described below.

5.3.1 Design

The SANAD Neuropsychology study was a prospective, multicentre, longitudinal study.

5.3.2 Recruitment

Patients with epilepsy

At the time of randomisation into the SANAD trial, previously untreated patients with newly diagnosed epilepsy from 11 hospital centres were invited to participate in the SANAD Neuropsychology study (see Table 5.2).

Table 5.2: Centres involved in the SANAD Neuropsychology study

- Doncaster Royal Infirmary, Doncaster
- Glan Clwyd Hospital, Bodelwyddan
- Hope Hospital, Salford
- Leigh Infirmary, Leigh
- Royal Bolton Hospital, Bolton
- Royal Hallamshire Hospital, Sheffield
- Royal Victoria Infirmary, Newcastle upon Tyne
- University Hospital of Wales, Cardiff
- Walton Centre for Neurology and Neurosurgery, Liverpool
- Whiston Hospital, Prescot
- Wrexham Maelor Hospital, Wrexham

These centres were chosen as they were either the most active recruiting centres in SANAD or the most local hospital centres to Liverpool. Patients with epilepsy were recruited between October 2000 and August 2004.

Inclusion/exclusion criteria

Patients were recruited into the SANAD Neuropsychology study if they met the inclusion criteria for the SANAD trial; they were previously untreated adults with newly diagnosed epilepsy and they gave informed consent. Patients were excluded if they had previously taken antiepileptic drugs or they were aged less than 15yrs.

Healthy volunteers

Healthy volunteers from the general population were recruited to act as a non-epilepsy reference group. Unfortunately, due to a lack of resources (both time and financial), this healthy volunteer group was unable to be collected at the same time as the SANAD

Neuropsychology patients. However, as a reference control group was thought to be necessary to assess the effects of epilepsy and its treatment on cognition, this was collected by the author at a later date. The healthy volunteers were recruited between March 2007 and October 2007.

There were three main reasons why a reference control group was thought to be necessary:

- Healthy volunteers from the general population have been used as a comparison group in several similar studies (Smith *et al.*, 1987, Kalviainen *et al.*, 1992, Aikia *et al.*, 1995, 2001, Prevey *et al.*, 1998, Pulliainen *et al.*, 2000, Salinksy *et al.*, 2002, 2004, 2005).
- The use of a healthy volunteer group means that patients with epilepsy can be compared with their peers to see if they already differ in terms of their cognitive functioning at the time of diagnosis.
- The use of a healthy control group, assessed at baseline and 12 months, provides an estimate of the test-retest effects of the neuropsychological test battery (Salinsky *et al.*, 2001). Their performance can then be used to create regression equations, which are applied to the patient's performance to evaluate the clinical significance of any observed cognitive change (see section on 'Standardised regression-based change scores in section 5.5.3).

The healthy volunteers were recruited by opportunity sampling. Efforts were made to equate them in terms of sex and age to the epilepsy group. The majority were friends and family of the researchers; some were friends and family of work colleagues; some were non-medical staff at the Walton Centre for Neurology and Neurosurgery and some were undergraduate students at the University of Liverpool.

Inclusion/exclusion criteria

The healthy volunteers were entered into the study if: they were aged over 15 years; they were matched in age and sex to one of the patient's with epilepsy; they felt they would be available to complete the 12 month assessment and they had given informed consent.

Healthy volunteers were excluded if they had a previous neurological or psychiatric history or had previous use of antiepileptic drugs or a history of substance abuse.

Neurological and psychiatric history was assessed informally by self-report in a semi-structured interview prior to assessment, for example, healthy volunteers were asked if they had ever been treated for anxiety or depression; had ever had a previous head injury or neurological disorder. These exclusion criteria were chosen as these may have influenced the cognitive functioning of individuals in the healthy volunteer group and the aim of the study was to compare newly diagnosed people with epilepsy to healthy people from the general population.

5.3.3 Power calculation

The power calculation for the SANAD Neuropsychology study was based on the original aim of detecting differences in cognitive functioning between standard and new AEDs. A power calculation revealed that 50 patients were needed in each drug group, to detect a mean difference of ½ standard deviation (SD) on the Finger Tapping task between the groups, setting the power at .80 and probability of making a Type 1 error at p=.05 (see original protocol in Appendix A). The numbers who were recruited and remained on their randomised drug in each drug group fell short of this and so the study was underpowered to detect the differential effects of AEDs.

However, for the purposes of this thesis, the aim was to detect differences between the two groups at baseline (patients and healthy volunteers). Therefore, the number of healthy volunteers recruited into the study was based on a separate sample size calculation. This was based on the finger tapping task for three reasons:

- It is one of the most frequently used tests employed in randomised clinical trials in epilepsy (Cochrane *et al.*, 1998, Baker & Marson, 2001). It is also one of the most commonly used tests by neuropsychologists. In a survey in the USA, it came sixth among the top 20 tests (Camara *et al.*, 2000).

- It is thought to be sensitive to changes in functioning in people with epilepsy and has shown statistically significant cognitive effects of AEDs (Cochrane *et al.*, 1998, Baker & Marson, 2001).
- It was used as the main outcome measure in the power calculation for the SANAD Neuropsychology study.

This power calculation was carried out by Dr Ruwanthi Kolamunnage-Dona and Dr Catrin Tudur-Smith at the Centre for Medical Statistics and Health Evaluation (CMSHE) at the University of Liverpool. To have a power of at least 80% to detect a difference of approximately one third standard deviations between the two groups (patients and control), 87 healthy controls were needed.

5.3.4 Ethical approval

The SANAD Neuropsychology study received ethical approval from the North West Research Ethics Committee in June 2000, as an amendment to the SANAD trial (Ref: MREC 98/8/62). Ethical approval to recruit and assess healthy volunteers was granted separately and was approved by the North West Research Ethics Committee in October 2006 (Ref: 06/MRE08/51). All participants gave written informed consent.

5.3.5 Procedure

Patients with epilepsy

Patients with newly diagnosed epilepsy were recruited at the time of randomisation into SANAD. They were assessed before the start of antiepileptic drug medication using a comprehensive battery of neuropsychological tests (details of the battery will be provided in section 5.3.6). As part of the SANAD Neuropsychology study, patients were re-assessed after three months in order to assess the cognitive effects of AEDs in the short term. However, as this thesis will not focus on AED differences, this data will not be reported here. Before their 12 month assessment was due, patients were contacted by either letter or telephone, to arrange their 12 month assessment. Again, they were re-assessed using the same battery of neuropsychological tests. Patients were assessed either at their home or in their local hospital

at the same time as their SANAD follow-up appointments. They were recruited and assessed by trained research assistants employed at the various recruiting centres.

Healthy volunteers

Healthy volunteers were approached by the researchers to see if they wanted to take part in the study and they were provided with participant information sheets. If they gave informed consent, they were assessed, using the same battery of neuropsychological tests, as a baseline measure. After 11 months, healthy volunteers were re-contacted, by either letter or telephone, to arrange their 12 month appointment. The healthy volunteers were assessed either at home or at a place that was most convenient for them (for example, seven were assessed at work and three at the University of Liverpool).

The author was responsible for recruiting and assessing the healthy volunteer group and was assisted by an undergraduate psychology student, as part of a third year undergraduate project. The author completed 112 (72%) assessments personally, which represents approximately 170 hours of direct assessment and 112 hours of scoring. The author was also responsible for training the undergraduate on administering the neuropsychological test battery and for checking their assessments to ensure that scoring was accurate and standardised.

5.3.6 Neuropsychological test battery

The neuropsychological test battery for the SANAD Neuropsychology study was chosen based on the recommendations of an International Cognitive Function Expert Panel which met in the USA in April 1996 (see original protocol in Appendix A). The battery comprised measures from the FePsy computerised test program (Alpherts, 1987) as well as traditional paper and pencil measures. As shown in Table 5.3, the test battery aimed to assess a wide variety of cognitive domains measuring both objective and subjective cognitive functioning. Each of the tests was selected on the basis of their proven reliability, validity and use in people with epilepsy (Cochrane *et al.*, 1998, Baker & Marson, 2001).

Table 5.3: Neuropsychological test battery

Domain	Test	Reference	Outcome variable
Psychomotor speed	Finger tapping	(Alpherts, 1987)	• The average number of taps for the dominant and non-dominant hand across five trials
	Visual reaction time	(Alpherts, 1987)	• The average reaction time for the dominant and non-dominant hand (in milliseconds)
	AMIPB psychomotor speed	(Coughlan & Hallows, 1985)	• The mean number of digits crossed through over two trials
Memory	Recognition of words/figures	(Alpherts, 1987)	• The number of words or figures correctly answered on the serial/simultaneous version of the task
	Rey Auditory Verbal Learning Task	(Rey, 1964)	• The sum of words recalled over the five trials and the number of words recalled after a 30-min delay
	Story recall	(Wilson *et al.*, 1989)	• The number of story units recalled immediately and after a 10-min delay
Information processing	AMIPB information processing	Coughlan & Hallows (1985)	• The mean number of correct responses over the two tasks
	Binary choice reaction time	(Alpherts, 1987)	• The average response speed (in milliseconds)
	Computerised Visual Search Task	(Alpherts, 1987)	• The average speed of response (in seconds)
Mental flexibility	Stroop	(Trenerry *et al.*, 1989)	• The number of correct responses on the colour-word task
	Benton verbal fluency	(Benton & Hamsher, 1976)	• The total number of acceptable words produced
Mood	Profile of Mood State	(McNair *et al.*, 1992)	• Transformed scores (/100) for each mood factor
Subjective report of cognitive complaints	Aldenkamp-Baker Neuropsychological Assessment Schedule	(Aldenkamp *et al.*, 1995)	• Transformed scores (/100) for each sub-scale

AMIPB=Adult Memory and Information Processing Battery

FePsy computerised test program

The FePsy computerised test program was originally developed in the Netherlands in 1978 for the psychological assessment of people with epilepsy. In 1984, a computerised neuropsychological test battery was developed for use in both adults and children (aged over

8 years) with epilepsy (Moerland *et al.*, 1986, 1988). It compromises a number of different tasks that measures aspects of attention and concentration, memory, information processing, motor speed and reaction time. The FePsy was chosen for use in this study for several reasons, as shown in Table 5.4. Five tests were selected from the program because they are the most commonly used [Computerised Visual Search task (CVST), Finger Tapping, Visual Reaction time (VRT), Binary Choice Reaction Time (BCRT) and Recognition of words and figures].

Table 5.4: Reasons for the use of the FePsy computerised test program

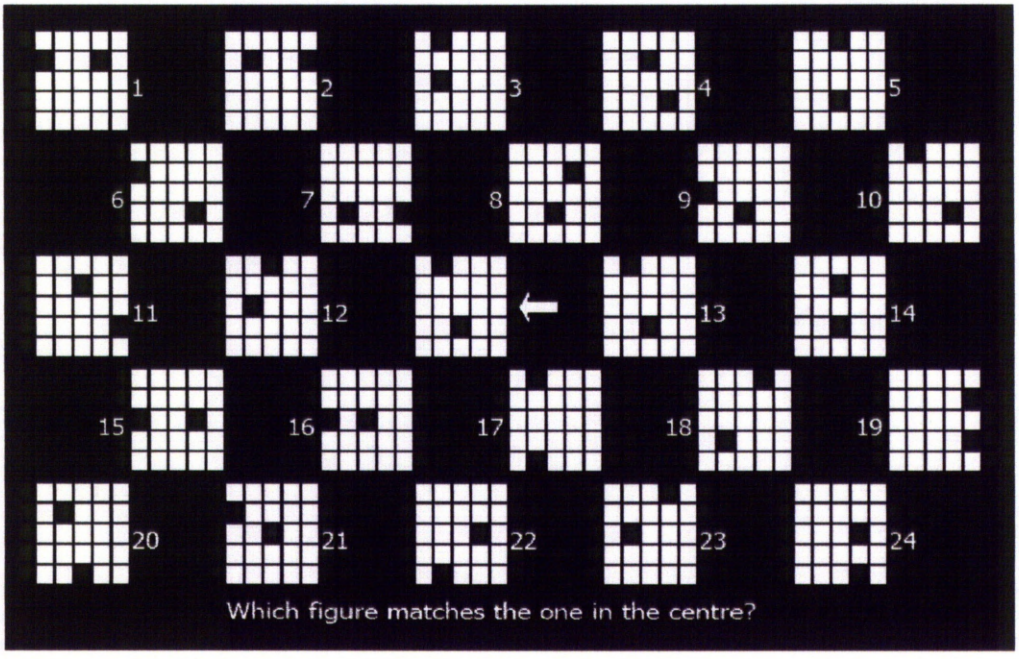
• It was developed *specifically* for use with PWE (Moerland *et al.*, 1986, 1988, Alpherts, 1987)
• It assesses domains of cognitive functioning known to be affected in epilepsy, for example, memory, psychomotor speed, attention and concentration (Alpherts, 1987, Moerland *et al.*, 1988)
• It is thought to be sensitive to detect subtle effects of AEDs (Aldenkamp *et al.*, 1987, Alpherts, 1987, Moerland *et al.*, 1988, Alpherts & Aldenkamp, 1990)
• It has been employed in several studies assessing the cognitive side effects of AEDs (Alpherts *et al.*, 1987, Aldenkamp *et al.*, 1987, 1993, 1997, 2000, 2002b, Sveinbjornsdottir *et al.*, 1994, Neyens *et al.*, 1995, Kalviainen *et al.*, 1996, Ogunrin *et al.*, 2005, Aldenkamp & Alpherts, 2006, Donati *et al.*, 2006, Pressler *et al.*, 2006, Aikia *et al.*, 2006b)
• Computerised assessments are highly standardised and limit the interaction between the examiner and participant, which is a potential source of bias. As several research assistants were involved in the administration of data, this was particularly relevant for this study (Moerland *et al.*, 1986, Strauss *et al.*, 2006)
• The recording of computerised data is automatic and very accurate (can be measured in milliseconds) so scoring and administration errors are reduced (Alpherts & Aldenkamp, 1990)
• Test items are selected randomly from a pool of items to reduce practice effects (Moerland *et al.*, 1986, 1988)
• It has been shown to have reliability and validity even when used to assess PWE several times in one day (Aldenkamp *et al.*, 1987)

Computerised Visual Search Task

This task, adapted from Goldstein's visual searching task (Goldstein *et al.*, 1973), aims to assess information processing and perceptual-visual skills. The participant is presented with 24 patterns on the screen with an arrow pointing to a target pattern in the centre of the screen, as shown in Figure 5.3. The participant is asked to find the pattern that is identical to the target pattern. The participant is asked to respond as quickly as possible. If the participant correctly identifies the matching pattern (e.g. '13'), a new one is presented. If they are incorrect, they have to re-try until they get the answer correct. The participant has three

practice trials before they have a total of 24 different patterns to match. The outcome variable is the average speed of response, measured as the average time taken (in seconds), to correctly find the identical pattern.

Figure 5.3: An example from the Computerised Visual Search Task



Finger tapping

This task, adapted from the Halstead-Reitan battery, aims to assess psychomotor speed and motor fluency. The participant is asked to tap with their index finger on the space bar of the keyboard as quickly as possible for 10 seconds. Tapping speed is measured for each hand. The participant is told to tap with their dominant index finger first (for 10 seconds); then their non-dominant index finger (for 10 seconds) and then alternate until they have tapped 10 times in total (five times each hand). Feedback is provided on the screen. There is a counter in the centre and the number of taps obtained on previous trials is recorded across the bottom of the screen. The outcome variables are the average number of taps for the dominant and non-dominant hand across the five trials.

Visual Reaction Time

This task aims to assess alertness, speed of activation of the information processing system and psychomotor speed. The participant is asked to respond as quickly as possible, by pressing the space bar, when a white square appears in the middle of the screen. The interval between presentations of the white square is randomly varied between 2.5 and 4 seconds. The participant is asked to respond with their dominant hand first and then half-way through the task is asked to use their non-dominant hand. Reaction time is recorded for both hands separately. The outcome variables are the average reaction time for the dominant and non-dominant hand in milliseconds.

Binary Choice Reaction Time

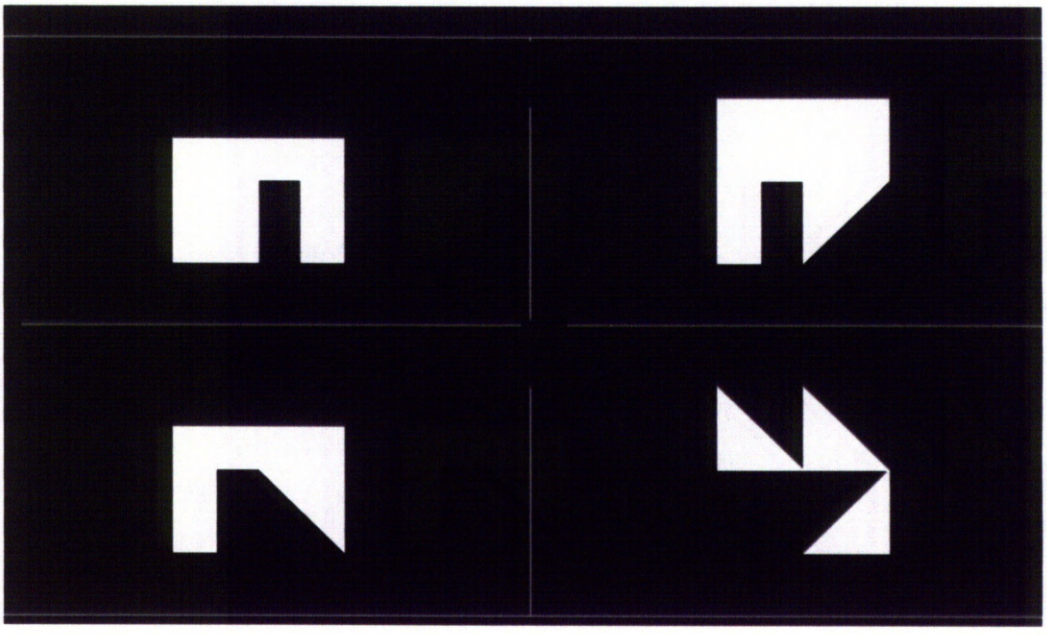
This task aims to assess information processing and attention. As this task comprises a decision-making component, it is more complex than the previously described simple visual reaction time task. The participant is asked to respond as quickly as possible when a block appears on the screen. When a red block appears on the right hand side of the screen, they have to press a key with their right hand and if a green block appears on the left side of the screen, they have to press a key with their left hand. The blocks appear on the left or right side in a random sequence. The task is self-paced and continuous. A new block appears instantly after the participant has responded to the previous one. The participant has an initial practice phase before they are presented with 60 stimuli. The outcome variable is the average response speed in milliseconds.

Recognition of words and figures

This task assesses recognition memory of both verbal and visual stimuli. The task is divided into four versions depending on the study material to be remembered (words vs. figures) and the presentation of study material (simultaneous vs. serial). However, due to technical problems with the simultaneous recognition of figures task (e.g. program crashing/freezing), the results of this particular task were considered to be both inaccurate and incomplete. Therefore, only the three other tasks will be described and reported on. The words to be remembered are four-letter words, which are randomly selected from a pool of 100 words.

The figures are randomly built from basic shapes (e.g. triangles and shapes) and are difficult to verbalise, as shown in Figure 5.4.

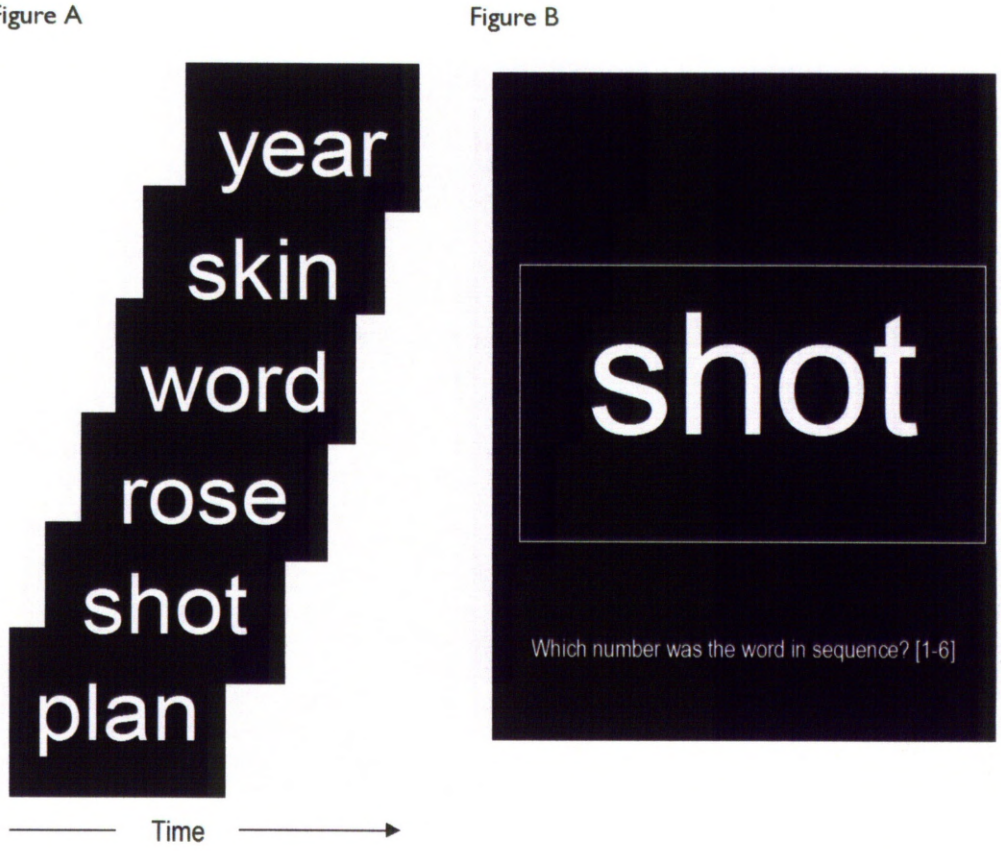
Figure 5.4: Examples of the visual stimuli used in the serial recognition of figures task



Serial recognition of words

Figure 5.5 illustrates the serial recognition of words task. In the study phase, the participant is presented with six words that appear one after the other in the centre of the screen at a rate of one per second (see Figure A). The participant is asked to remember the order in which the words appeared. After two seconds, one of the six words appears again and the participant has to type in the order of presentation of that word in the study phase (see Figure B). For example, 'shot' was the second word that appeared, so they would type '2'. No feedback is provided. There is an initial practice phase of three trials. The outcome variable is the number of words correctly answered out of 24 trials.

Figure 5.5: An example of the serial recognition of words task. Figure A represents the study phase. Figure B represents the test phase



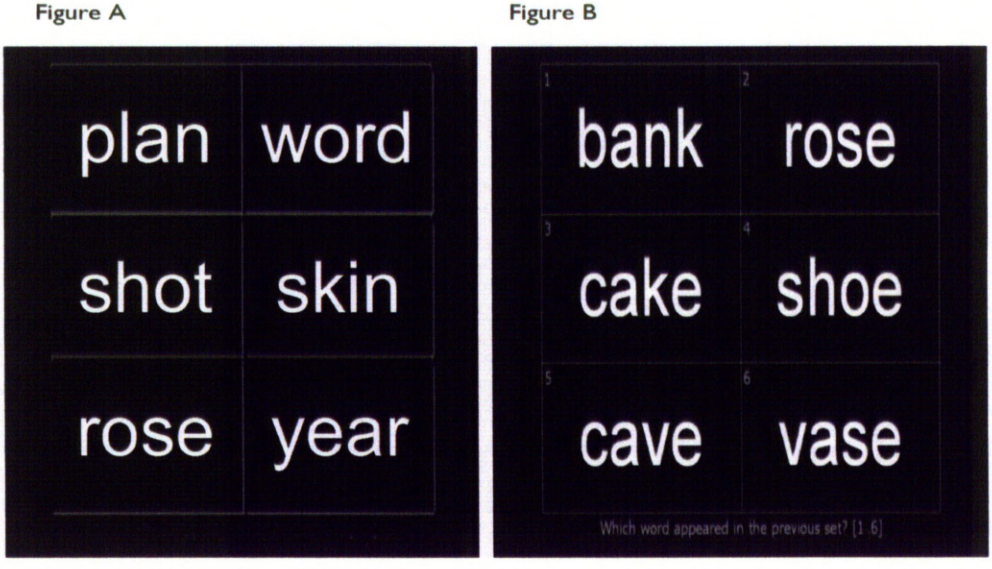
Serial recognition of figures

This task is the non-verbal equivalent of the serial recognition of words task described above. In the study phase, the participant is presented with four figures that appear one after the other in the centre of the screen at a rate of one per second. The participant is asked to remember the order in which the figures appeared. After two seconds, one of the four figures appears again and the participant has to type in the order of presentation of that figure in the study phase. No feedback is provided. There is an initial practice phase of three trials. The outcome variable is the number of figures correctly answered out of 24 trials.

Simultaneous recognition of words

As shown in Figure 5.6, in the study phase, the participant is presented with six words that appear on the screen at the same time for six seconds (see Figure A). The participant is asked to remember all of them. After two seconds, a second set of six words are presented containing one of the words from the previous set (see Figure B). The participant has to correctly identify which of these words was in the study phase (e.g. rose, number '2'). There is an initial practice phase of three trials. The outcome variable is the number of words correctly identified out of 24 trials.

Figure 5.6: An example of the simultaneous recognition of words task. Figure A represents the study phase. Figure B represents the test phase



Paper and pencil neuropsychological tests

Traditional paper and pencil measures were also used along with the FePsy computerised test battery to obtain a comprehensive assessment of cognitive functioning (see Appendix B). These remaining tests were chosen because they have good reliability and validity and have previously been used in studies with people with epilepsy. For the purposes of this thesis, in evaluating the reliability of a test, those with reliability coefficients >.80 were considered to

have high levels of reliability and those with >.70 were considered to have adequate and acceptable levels for research (Strauss *et al.*, 2006).

Rey Auditory Verbal Learning Test (RAVLT)

This task aims to assess verbal memory and learning (Strauss *et al.*, 2006). It has been developed for use in individuals aged between 6-89 years (Rey, 1964). The participant is presented with a list of 15 unrelated words which are read aloud by the examiner at a rate of one per second. The participant is then asked to free recall as many of the words as they can remember. The list is read a second time and again the participant has to free recall as many words as they can remember, including the words they have said previously. This is repeated until the list has been read aloud five times. The participant is then asked to remember the list, as they will be asked to recall it later. After a 30 minute delay, the participant is asked to free recall as many words as they can from the original list without being presented with it again. The outcome variables are: the sum of the words recalled over the five trials, as a measure of immediate memory and total acquisition; and the number of words recalled after a 30 minute delay, as a measure of delayed recall.

Alternate parallel forms, developed by Crawford, Stewart and Moore (1989), are available for this task and different versions of the list were used at each assessment. This has been shown to reduce practice effects (Crawford *et al.*, 1989, Lemay *et al.*, 2004).

This test has adequate test-retest reliability. After a one month test-retest interval using the alternate forms, correlations for the different outcome measures ranged between 0.61-0.86 (Delaney *et al.*, 1992). After one year, correlations coefficients were not as high, but ranged from .60-.70 (Mitrushina & Satz, 1991). The test also has good validity, correlating with other measures of learning and memory such as the Wechsler Memory Scale-Revised (WMS-R) Logical Memory subscale (Johnstone *et al.*, 2000) and the California Verbal Learning Test (Crosson & Wiens, 1994). This task has been used in other studies assessing the cognitive side effects of antiepileptic drugs (e.g. Dodrill *et al.*, 1993, 1995, 1997, 1999, 2000, Prevey *et al.*, 1996, Blum *et al.*, 2006, Donati *et al.*, 2006).

Story recall

Recall of stories or short paragraphs have been used in several studies assessing cognitive functioning in people with epilepsy (e.g. Curran & Java, 1993, Craig & Tallis, 1994, Grunewald *et al.,* 1994, Kalviainen *et al.,* 1995, 1996, Meador *et al.,* 1995, 1999, 2001, 2005, 2007, Martin *et al.,* 2001, Salinksy *et al.,* 2002, 2004, 2005, Aikia *et al.,* 2006b; Bum *et al.,* 2006). These tasks are designed to resemble everyday verbal memory functioning (Lezak *et al.,* 2004, Strauss *et al.,* 2006). The stories used in this study were taken from the story recall sub-test of the Rivermead Behavioural Memory Test, which has been developed for use in individuals aged between 11-94 years. This test was designed to have high ecological validity and the stories resemble news items containing British characters (Wilson *et al.,* 1989).

In this task, the participant is presented with a short story. After presentation of the story, the subject is asked to free recall as much of the story as they can remember. According to the scoring criteria, points are awarded for each piece of information correctly recalled and half points are awarded for partially correct information. The participant is then asked to remember the story as they will have to recall it later. After a ten minute delay, the participant has to free recall the story without hearing it again. Recall is scored using the same scoring system. A cue can be provided if the participant cannot remember any information from the story. The outcome variables are the immediate and delayed recall score.

Alternate parallel forms are available for this test and different versions of the story were used at each assessment. The test-retest reliability of the Rivermead Behavioural Memory Test battery is high (.89) when assessed in stroke patients over a two week period (Man & Li, 2001). But test-retest reliabilities for each individual sub-test are not available. The Rivermead Behavioural Test correlates with other tests of memory functioning, such as the Warrington Recognition Memory Test, Wechsler Memory Scale and Rey Auditory Verbal Learning Test (Strauss *et al.,* 2006).

Verbal fluency task

This task aims to assess the spontaneous production of words under restricted search conditions (Strauss *et al.,* 2006). The test has been developed for use in individuals aged

between 7-95 years (Benton & Hamsher, 1976). The participant is asked to generate as many words as possible beginning with three specified letters of the alphabet in 60 seconds. However, they have to follow three rules: they are not allowed to use proper nouns; numbers; or altered/extended versions of words. The outcome variable is the total number of acceptable words produced over the three letters.

Three alternate, parallel forms (FAS, CFL and PRW) have been developed by Benton & Hamsher (1976) and so these different versions were used for the baseline, three month and 12 month assessments. The first version (FAS) had to be re-administered in the follow-up study, however, as this was between three and seven years later, practice effects were considered to be small. After an interval of more than five years, test-retest reliability was .74 in elderly individuals (Tombaugh *et al.*, 1999). When alternate parallel versions are used, the test-retest reliability coefficient for 120 participants over an interval of six months was similar (.77) (Ruff *et al.*, 1996). In terms of validity, the verbal fluency task has been found to correlate with verbal IQ (Lacy *et al.*, 1996). Verbal fluency has been used in several studies to assess the cognitive side effects of AEDs (e.g. Curran & Java, 1993, Helmstaedter *et al.*, 1993, Dodrill *et al.*, 1993, 1995, 1997, Prevey *et al.*, 1996; Martin *et al.*, 1999, 2001, Aldenkamp *et al.*, 2000, Ojemann *et al.*, 2001, Salinsky *et al.*, 2005).

Stroop Neuropsychological Screening Test

This task aims to assess attention and concentration as well as the ability to inhibit responses and ignore distracting stimuli. The version used was that developed by Trenerry *et al.* (1989). In the first part of the task, the colour task, the participant is presented with a list of 112 colour words (red, blue, green, tan) which they have to read aloud as fast as they can. The participant has two minutes to respond. The second part of the task is the colour-word task. The participant is presented with the same 112 colour words printed in conflicting ink colours. The participant is asked to name the colour of the ink that the word is printed in rather than read the words. The participant has two minutes to complete the task. This task was not administered to those who reported being colour-blind [7 (3.1%) patients with epilepsy and 3 (3.4%) healthy volunteers]. The outcome variable is the number of ink colours correctly named on the colour-word task within the two minutes.

The normative data for the Stroop Neuropsychological Screening Test is based on 156 adults aged between 18-79 years. There are age differences in performance on the colour-word task and so normative data is divided into those aged above/below 50 years (Trenerry *et al.*, 1989). The normative sample was used to derive percentiles, with lower percentiles indicating greater difficulty on this task. Separate percentiles were derived for those aged 18-49yrs and those aged over 50yrs. The high test-reliability correlation coefficient (.90) was assessed by retesting 30 participants in the normative sample over an average of 59 days interval. There are no alternate forms of this task and practice effects were observed over the 59 day interval, with an approximate 5% increase from baseline (Trenerry *et al.*, 1989).

The Stroop Neuropsychological Screening Test was validated in patients with left- and right-hemisphere cerebrovascular accidents; closed head injuries and other central nervous system disorders. The test was able to correctly classify 79% of those aged under 50 years as either 'brain-damaged' or from the 'normative' sample and correctly classify 91.8% of those aged over 50 years. The Stroop Neuropsychological Test correlated, as was expected, with other tests, for example Category Test errors (-.57); Wechsler Adult Intelligence Scale-Revised (WAIS-R) Full scale IQ (.46); Verbal IQ (.44); Performance IQ (.49); WAIS-R Block Design (.77) and Vocabulary scores (.31) (Trenerry *et al.*, 1989). The Stroop task is the most commonly used task in randomised clinical trials in epilepsy (Cochrane *et al.*, 1998, Baker & Marson, 2001), however, the particular version used is not always stated.

Adult Memory and Information Processing Battery (AMIPB)

The Adult Memory and Information Processing Battery (AMIPB) comprises a series of memory and information processing tasks (Coughlan & Hallows, 1985). Two sub-tests from the AMIPB were selected for their ability to measure psychomotor speed and information processing.

Psychomotor speed

In this task, the participant is presented with three columns containing 11s and is asked to cross through the 11s as fast as they can. They have 20 seconds to work as quickly as

possible. This task is completed twice and the outcome variable is the mean number of 11s crossed through over the two trials.

Information processing

This task is thought to measure performance on timed, repetitive, mentally engaging activities (Coughlan & Hallows, 1985). Performance on this task is thought to be independent of memory skills or general intelligence but is sensitive to cerebral dysfunction (Coughlan & Hallows, 1985). This task comprises two similar cancellation tasks (A and B). In task A, the participant is presented with a page containing 105 rows of numbers. Each row is made up of five two-digit numbers (e.g. 28, 16, 49, 21, 72). The participant is asked to cross out the second highest number in each row e.g. 49. There are five demonstration items and five practice items to ensure that the participant has understood the task. The participant has four minutes to work through as many rows as possible. They are told to work as quickly and as accurately as possible.

In task B, the participant is presented with a similar page containing 105 rows of numbers. Each row comprises nine numbers separated by a hyphen, with four on the left side and five on the right side (e.g. 2 8 7 1 – 4 8 2 1 7). The participant is asked to cross out the number on the right side that does not appear on the left side (e.g. 4). There are five demonstration times and five practice items to ensure that the participant has understood the task. The participant has four minutes to work through as many rows as possible. They are told to work as quickly and as accurately as possible. Two alternate versions of this task (Form 1 and Form 2) are available and these were used alternately at each assessment. The outcome variable is the mean number of correct responses within four minutes over the two tasks.

Each form of the Adult Memory and Information Processing Battery was standardised on 180 healthy volunteers from the UK. Test-retest reliability was assessed in 30 subjects tested between 1-6 days, who were given a different form at their second assessment. Test-rest reliability for the information processing tasks was high (.79 for Task A and .89 for Task B). Test-retest reliabilities for psychomotor speed were also high (.83 for Task A and .81 for Task B) (Coughlan & Hallows, 1985).

The test was validated by comparing the data from the normative sample with 54 patients with generalised cerebral dysfunction (e.g. severe head injury defined as post-traumatic amnesia > 7 days; encephalitis; cerebral atrophy; raised intracranial pressure and acute vitamin deficiency). The patients scored significantly lower on both the information processing (p<.001) and psychomotor speed tasks (p<.001).This task has been also been used in studies comparing the cognitive side effects of AEDs (e.g. Sveinbjornsdottir *et al.,* 1994, Grunewald *et al.,* 1994).

Profile of Mood States (POMS)

This self-report questionnaire, revised by McNair *et al.,* (1992), aims to assess participant's current mood state. The questionnaire comprises 65 adjectives that describe feelings. For each item, the participant is asked to rate how often they have felt like that over 'the past week including today' using a five point scale (0=not at all to 4=extremely). The POMS assesses six mood factors: Tension-Anxiety; Depression-Dejection; Anger-Hostility; Vigour-Activity; Fatigue-Inertia; Confusion-Bewilderment (see Table 5.5).

Table 5.5: Example of items on the Profile of Mood States questionnaire

Mood factor	Description	Example items	No of items	Range of scores
Tension-Anxiety	Heightened musculoskeletal tension	Tense, shaky, on edge	9	0-36
Depression-Dejection	Depression accompanied by a sense of personal inadequacy	Unworthy, hopeless, guilty	15	0-60
Anger-Hostility	Anger and antipathy towards others	Grouchy, resentful, spiteful	12	0-48
Vigour-Activity	Vigorousness, ebullience and high energy	Lively, active, energetic	8	0-32
Fatigue-Inertia	Weariness, inertia and low energy level	Listless, exhausted, sluggish	7	0-28
Confusion-Bewilderment	Bewilderment and muddle headedness	Confused, unable to concentrate, muddled	7	0-28

Scores for each mood factor are calculated by summing the participant's responses to the appropriate items. Based on normative data, raw scores can be converted into standardised *T* scores (mean=50, SD=10) by plotting scores onto the POMS profile sheet, which is available

for psychiatric outpatient males and females and a healthy college sample. However, it is recommended that raw scores are used for research purposes, as the standardised scores remove any potential sex differences, therefore the raw scores were used in this study (McNair *et al.,* 1992). As each mood factor is made up of a different numbers of items, for the purposes of this thesis, the raw scores were transformed to scores out of 100. This is to allow comparison across the sub-scales. This was calculated by: *(mood factor score/max possible score)*100.* The outcome variables are the transformed scores (out of 100) for each mood factor. A high score on each of the mood factors reflects higher mood disturbance except for the vigour factor, which is negatively weighted, so a higher score reflects greater energy and vigour.

The POMS mood factors have high internal reliability (.85-.95). However, its test-reliability after a median 20 days (3-110 days) in a sample of 100 patients from the psychiatric normative sample is marginal-adequate (.65-.74). After six weeks, test-retest reliability was low (.43-.53) (McNair *et al.,* 1992). Several validation studies have been undertaken on the POMS, which have provided evidence of the factorial validity of the six mood factors as well as its predictive, construct and concurrent validity (McNair *et al.,* 1992). The POMS has been used frequently in studies investigating the cognitive and behavioural effects of AEDs (e.g. Meador *et al.,* 1990, 1995, Dodrill *et al.*, 1993, 1997, 1999, 2000, Pulliainen & Jokelainen *et al.*, 1995; Martin *et al.,* 1999, 2001, Aldenkamp *et al.,* 2000, Salinsky *et al.*, 2002, 2004, 2005, Blum *et al.,* 2006).

Aldenkamp-Baker Neuropsychological Assessment Schedule (ABNAS)

This self-report questionnaire was designed to assess the subjective report of cognitive effects of antiepileptic drugs (Aldenkamp *et al.,* 1995, Aldenkamp & Baker, 1997, Brooks *et al.*, 2001). The questionnaire comprises 24 statements associated with difficulties in six cognitive domains: fatigue, slowing, memory, concentration, motor co-ordination and language. The participant is asked to rate on a four point scale (0=no problem to 3=serious problem) to what extent they agree with each statement (see Table 5.6).

Table 5.6: Example of items on the ABNAS

Sub-scale	Example item	No of items	Range of scores
Fatigue	I tire easily and have little energy	5	0-15
Slowing	My mind does not work as fast as it should	5	0-15
Memory	I have difficulties remembering names of people	4	0-12
Concentration	I have difficulties following a book or film	4	0-12
Motor	I feel clumsy	3	0-9
Language	I have problems finding the correct word	3	0-9
Total		**24**	**0-72**

Scores for each sub-scale are calculated by summing the participant's responses to the appropriate items. A total ABNAS score is calculated by summing the scores across all the sub-scales. As each sub-scale is made up of different numbers of items, for the purposes of this thesis, the raw scores were transformed to scores out of 100. This is to allow comparison across the sub-scales. This was calculated by: *(sub-scale/max possible score)*100.* The outcome variables are the transformed total ABNAS score and the transformed score (out of 100) for each sub-scale.

As this questionnaire was developed to assess the adverse effects of antiepileptic drugs on cognition and primarily for use in clinical trials (Aldenkamp *et al.,* 1995), it was only administered to the patients with epilepsy.

Test-retest reliability of the ABNAS has not been assessed formally; however, it is a reliable measure, with a high internal reliability [Cronbach's alpha .95 (Aldenkamp & Baker, 1997), .96 (Brooks *et al.,* 2001)]. The ABNAS has been validated in healthy volunteers as part of a double-blind placebo-controlled parallel group design, where participants were randomised to a benzodiazepine (temazepam 10mg or 20mg) or placebo (Aldenkamp *et al.*, 1995). It has also been validated for use in people with epilepsy (Aldenkamp & Baker, 1997, Brooks *et al.,* 2001). The ABNAS has been shown to be significantly correlated with the Adverse Events Profile; Hospital Anxiety and Depression Scale and Everyday Memory Questionnaire (Brooks *et al.,* 2001) and neuropsychological tests from the FePsy computerised test battery (Aldenkamp *et al.*, 2002b). It has also been used in several studies assessing the subjective

report of cognitive side effects of AEDs (Aldenkamp *et al.*, 1998, 2000, 2002a, Meador *et al.*, 2001, 2005, 2007, Blum *et al.*, 2006)

Administration

The neuropsychological test battery took approximately 1 ½ hours to complete. The tests were administered in a fixed order to ensure adequate time passed to test delayed recall on the memory tasks. However, regular breaks were offered and taken to reduce fatigue effects. Neuropsychological assessment was postponed and rearranged for a later date in those patients who reported having a seizure within 24 hours of the assessment. As described, parallel alternate forms were used, where available, in the follow-up sessions to reduce practice effects associated with repeat neuropsychological testing (Beglinger *et al.*, 2005).

5.4 Neuropsychology follow-up study

Patients with epilepsy, who took part in the SANAD Neuropsychology study, were invited to take part in a neuropsychology follow-up study. This study was designed to investigate the third objective of this thesis:

- To document the longer term effects of epilepsy and its treatment on cognitive functioning in people with newly diagnosed epilepsy.

The design, recruitment of participants and procedure for this study will be described below.

5.4.1 Design

This follow-up study was an observational longitudinal study investigating the cognitive profile of patients with epilepsy three to eight years after their diagnosis.

5.4.2 Recruitment

Patients with epilepsy who had completed the 12 month assessment as part of the SANAD Neuropsychology study were invited to take part in the follow-up assessment. As patients had

various reasons for not completing the 12 month assessment (see section 7.2.1), only those who had completed the study were invited to take part. The number of patients who completed the 12 month assessments at each of the hospital centres is shown in Table 5.7.

Table 5.7: Number of patients at each recruiting centre who had completed the 12 month SANAD assessment

Hospital centre	Number completed (n, %)
Walton Centre for Neurology and Neurosurgery, Liverpool	39 (67.2)
Royal Bolton Hospital, Bolton	32 (71.1)
University Hospital of Wales, Cardiff	30 (66.7)
Royal Hallamshire Hospital, Sheffield	12 (70.6)
Wrexham Maelor Hospital, Wrexham	11 (55.0)
Glan Clwyd Hospital, Bodelwyddan	8 (61.5)
Hope Hospital, Salford	8 (61.5)
Doncaster Royal Infirmary, Doncaster	4 (57.1)
Leigh Infirmary, Leigh	2 (66.7)
Whiston Hospital, Prescot	1 (100.0)
Total	**147 (66.2)**

Two hospital centres were not included in the follow-up study (Leigh Infirmary and Whiston Hospital), as they only had very few eligible patients at each site. Due to the lengthy time procedures involved in obtaining Research & Development approval at each NHS trust, particularly the process of obtaining honorary contracts, it was not considered an effective use of time and resources to apply for R&D approval within these trusts. Therefore, patients were recruited from the remaining eight hospital centres. Patients were recruited between November 2007 and November 2008.

Inclusion/exclusion criteria

Patients were approached to take part in the follow-up study if they had completed the 12 month assessment as part of the SANAD neuropsychology study; they still had a diagnosis of epilepsy and they gave informed consent. Patients were excluded from taking part in the study if they had undergone epilepsy surgery or they expressed a wish not to take part in any further research, which was recorded either at the end of the SANAD Neuropsychology study or through the SANAD Quality of Life study.

Those who had undergone epilepsy surgery were excluded from this study, as epilepsy surgery is associated with neuropsychological consequences (see section on Epilepsy surgery in section 3.3.2) and this thesis is concerned with the natural history of cognitive functioning in people with newly diagnosed epilepsy, without surgical intervention. Eligibility was checked by asking patients about their medical history informally in a semi-structured interview prior to the assessment.

5.4.3 Power calculation

The power calculation for this follow-up study was conducted by Dr Ruwanthi Kolamunnage-Dona and Dr Catrin Tudur Smith at the CMSHE at the University of Liverpool. The power calculation revealed that follow-up assessments for 95 patients with epilepsy were needed to detect a meaningful clinically significant change of 2.12 taps on the Finger Tapping task from baseline to follow-up, setting the power at 0.80, correlation of .491, and adjusting for a finite sample.

5.4.4 Ethical approval

The follow-up study was considered to be a separate study, rather than an amendment to the SANAD Neuropsychology study, and so ethical approval was granted separately (along with approval to assess the healthy volunteers). Ethical approval to follow up the patients with epilepsy was obtained and approved by the North West Research Ethics Committee in October 2006 (Ref: 06/MRE08/51). Research governance approval was obtained from the local R&D committees. All participants gave written informed consent.

5.4.5 Procedure

Up to date contact details were checked with the on-going SANAD quality of life study database and by contacting each of the hospital centres. This also ensured that letters were not sent to patients who may have died since their 12 month assessment. Invitation letters and patient information sheets were sent out to those patients who had completed the 12 month assessment and had up to date contact details.

Patients were asked to either contact the researcher by telephone or by returning a reply slip in the prepaid envelope, if they did or did not want to take part in the follow-up study. A follow-up letter and telephone calls were made to those patients who had not responded after one week. Half way through the recruitment period, a newsletter produced by the author, was also sent out with the follow-up letters. This was to try and maximise recruitment and the amount of data available for analysis.

If patients wanted to take part in the study, a mutually convenient time and place to complete the assessment was arranged. Patients were assessed either at home or at an outpatient department of their local hospital. Once they had given informed consent, a semi-structured interview was conducted to obtain up-to-date demographic and clinical information. This information included: current medication; current seizure frequency or how long they had been seizure free; whether they had any other medical or psychological problems since their 12 month assessment and socio-demographic characteristics such as, employment status and educational history.

Patients were then assessed using the same battery of neuropsychological tests. After their assessment, letters were sent to their GPs informing them of their participation in the research.

The author was responsible for recruiting and assessing the patients with epilepsy in the follow-up study and was assisted by a Trainee Clinical Psychologist, as part of a Clinical Psychology doctoral thesis. The author completed 43 (86%) assessments personally, which represents approximately 64.5 hours of direct assessment and 43 hours of scoring. The author was also responsible for training the Trainee Clinical Psychologist on administering the neuropsychological test battery; co-ordinating assessments including sending letters to patients and their GPs, and for checking the assessments to ensure that scoring was accurate and standardised.

After the follow-up assessment, some patients requested feedback on their neuropsychological test performance. Under the supervision of Professor Gus A Baker, feedback letters were written by the author outlining any changes in cognitive functioning from

baseline to the end of the follow-up study period. This included providing strategies to help with memory functioning, where appropriate. If necessary, letters were sent to the patient's GP informing them of any significant changes or concerns.

5.5 Data entry and statistical analysis

The assessments for both the patients with epilepsy and healthy volunteers at all time points (baseline, 12 months and follow-up) were scored according to the scoring criteria set out in the test manuals. They were checked by two trained research assistants and entered onto a Statistical Package for Social Sciences (SPSS) database (version 16.0). Confidentiality was ensured by providing participants with a unique code, which was used on databases and record sheets. No other identifying information was stored alongside the data collected by the researchers. At the end of the data collection in November 2008, the whole database was checked and audited by the author to ensure accuracy of data entry.

The author conducted all the statistical analysis but advice was sought from Dr Ruwanthi Kolammunage-Dona at the CMSHE at the University of Liverpool. All data was analysed using SPSS version 16.0 and Stats Direct 2.6.8. The author was responsible for the interpretation of this data.

The results are divided into three separate results chapters answering each of the three objectives of this thesis. Therefore, the statistical analysis that was conducted on the data will be described in three separate sections below (sections 5.5.2, 5.5.3 and 5.5.4). As there are various methods which can be used to assess change in cognitive functioning over time, a brief description of these methods and justification for their use is provided in the section on 'Measuring change' in section 5.5.3.

5.5.1 Checking outliers

Before analysing the neuropsychological test data, raw scores on all test variables at all time points, were checked for the presence of outliers. These were defined as scores that fell more than three standard deviations above or below the mean. Three standard deviations is a

criterion that has been used in several similar studies (e.g. Oyegbile *et al.*, 2004, Hermann *et al.*, 2007a). Each outlier was checked to see if it was a genuine result or a recording error. If it was a recording error, then the score was corrected on the database. However, the majority of outliers were considered to be due to measurement error, particularly on the FePsy computer tasks (e.g. the tapping task had not recorded the numbers of taps correctly on a trial). These scores were deleted. In total, 113 outliers were removed from the dataset (113/13 350), which represents 0.8% of the data.

5.5.2 Statistical analysis for chapter 6

Demographic and clinical characteristics

Descriptive statistics were used to describe the demographic and clinical characteristics of the patients with epilepsy and healthy volunteers who were assessed at baseline. Independent *t* tests and chi square tests were carried out to investigate any differences in characteristics between the two groups.

Neuropsychological and psychological test data

Assessing the spread of the data

The raw scores on each of the measures were assessed to see whether they met the assumption of normality. The spread of the data was assessed by visually inspecting histograms, Q-Q plots, the values of skewness and kurtosis for each test variable and the results of the Kolmogorov-Smirnov test.

For the neuropsychological test variables, 11 of the 17 neuropsychological test variables did not differ from the normal distribution and so parametric analyses (independent *t* tests) were conducted on these. However, VRT (both dominant and nondominant hand), BCRT and CVST were positively skewed. Reaction time data is often skewed because there is a limit to how quickly an individual can respond to a stimulus but no limit to how slowly an individual can respond (Alpherts & Aldenkamp, 1990, Strauss *et al.*, 2006). Simultaneous recognition of words and the Stroop test were negatively skewed. A low ceiling was observed on the Stroop

colour–word task, with the majority of patients and healthy volunteers achieving maximum scores.

Due to the low ceiling effect observed on the Stroop Neuropsychological Screening Test, this variable was converted to a categorical one based on normative data (Trenerry *et al.,* 1985). Using the age-adjusted percentile, an individual was classified as falling within the borderline range if their score fell below the 10th percentile; in the low average range if their score fell between the 10th and 25th percentile; and in the average range if they performed above the 25th percentile. Chi square analysis was then applied to test differences between the two groups.

Log transformations were carried out on the five skewed variables, so that they met the assumption of normality for parametric analysis. However, scores on the BCRT and simultaneous recognition of words became more skewed after transformations so log transformations were only performed for the two VRT measures and CVST. Therefore, to test significant differences between the two groups, non-parametric (Mann Whitney) tests were carried out on the binary choice reaction time and simultaneous recognition of words.

For the mood variables, tension, depression, anger, fatigue and confusion were positively skewed. Only the vigour mood factor was normally distributed. As several participants had a score of zero, log transformations could not be carried out on these variables. Therefore, non-parametric (Mann Whitney) analyses were carried out on the mood factor scores to test differences between groups. To maintain consistency within the POMS, non-parametric analyses were also applied to the vigour factor, despite it meeting the assumptions of normality for parametric analysis. For the ABNAS scales, all sub-scales were positively skewed so box and whisker plots were used to present the data.

Age, sex and education adjusted z-scores

Raw scores on the 14 normally distributed neuropsychological test variables were converted to z-scores adjusted for age, sex and education relative to the control mean [Mean (M)=0, SD=1] using multiple regression techniques. This method has been employed in previous

studies involving adults with epilepsy (Oyegbile *et al.*, 2004, Hermann *et al.*, 2007a), children with epilepsy (Hermann *et al.*, 2006a) and those with early, untreated Parkinson's disease (Aarsland *et al.*, 2009). This method was used because it corrects for the effects of age, sex and education, which are important potentially confounding variables on cognitive functioning. Additionally, by putting all scores on a common metric, comparisons across tests and across domains can be made directly (Oyegbile *et al.*, 2004, Hermann *et al.*, 2006b, 2007a).

Using the healthy volunteers as a reference group, multiple regression techniques were used to create regression equations (see Table C.1). The regression equations regressed age, sex and education on baseline score. Age in years was entered as a continuous variable, sex as a dichotomous variable (0=female, 1=male) and education was divided into three categories (low ≤11yrs, medium 12-15yrs, high >15yrs). Two dummy variables were created so education could be entered into the regression. These equations were then applied to the patients with epilepsy to obtain age, sex and education predicted scores. The adjusted *z*-scores were calculated by applying the formula: [*(observed score-predicted score)/Standard Error estimate of the regression equation*]. The adjusted *z*-scores were transformed by multiplying the timed tasks by minus one, so that higher scores on all tasks reflected better performance (Temkin *et al.*, 1999).

Investigating relationships

Spearman's correlational analyses were carried out to investigate the relationship between neuropsychological test performance and previous seizure activity. One-way between subjects analysis of variance (ANOVAs) were carried out on each of the cognitive measures to investigate potential differences in epilepsy type. Spearman's correlations were performed to assess the relationship between cognitive test performance and mood.

Individual-level analysis

To investigate the clinical significance of results, the adjusted *z*-scores were used to identify individuals who demonstrated abnormal performance across the test battery. Abnormal performance was defined either as an adjusted *z*-score of ≤-1.5 or ≤-2.0.

A summary impairment index was created, which represents the proportion of test scores (from a total of 14) that are classified as abnormal. This reflects the degree of cognitive impairment exhibited by each individual (Oyegbile *et al.*, 2004, Hermann *et al.*, 2006b, 2007a). Exploratory analyses (using independent *t*, Mann Whitney and chi square tests) were conducted to try and identify the characteristics of those who were classified as impaired based on the impairment index. Impairment was defined as more than one abnormal test performance across the neuropsychological test battery. For this analysis, the more conservative value of $z \leq -2.0$ was used. Several studies have classified performance of more than two standard deviations below the control mean as abnormal (Oyegbile *et al.*, 2004, Hermann *et al.*, 2006b, 2007a). Finally, odds ratios were calculated to see if baseline cognitive impairment was a predictor of recurrent seizures at 12 months and longer term follow-up.

5.5.3 Statistical analysis for chapter 7

Demographic and clinical characteristics

Descriptive statistics were used to describe the demographic and clinical characteristics of the patients with epilepsy and healthy volunteers who were assessed at baseline and 12 months. Independent *t* tests, Mann Whitney tests and chi square tests were carried out to investigate any differences in demographics between the patients with epilepsy and healthy volunteers. These were also carried out to see if there were differences in demographic, clinical and baseline neuropsychological characteristics between those who did or did not respond at 12 months. However, for some of the variables, expected frequency counts for were less than five, so chi square analysis could not be carried out. Descriptives were provided instead.

Neuropsychological and psychological test data

Assessing the spread of the data

The raw scores and the difference scores between baseline and 12 months on each of the measures were assessed to see whether they met the assumption of normality. The spread of

the data was assessed by visually inspecting histograms, Q-Q plots, the values of skewness and kurtosis for each test variable and the results of the Kolmogorov-Smirnov test.

Fifteen of the 17 neuropsychological change scores did not differ from the normal distribution so paired *t* tests were carried out on these variables to investigate changes from baseline to 12 months in both groups. VRT with the non-dominant hand differed from the normal distribution in the patient group so Wilcoxon sign tests were carried out on this variable. Change scores on the Stroop colour-word task also differed from the normal distribution, however, because of the low ceiling observed on this task, this was converted to a categorical variable using the procedure described in section 5.5.2. Descriptive statistics were then used to describe the proportion of patients in each category at baseline and 12 months.

The 12 month neuropsychological variables were also assessed to see if they met the assumption of normality for use as criterion variables in the creation of standardised regression-based *z*-scores (see section on 'Measuring change' below). Twelve of the 17 variables did not differ from the normal distribution but five variables did not meet the assumption of normality. VRT with both the dominant and non-dominant hand and the CVST were positively skewed. The simultaneous recognition of words was negatively skewed and a low ceiling was observed on the Stroop colour-word task. Log transformations were carried out on the skewed variables, so that they met the assumption of normality for parametric analysis. However, simultaneous recognition of words became more skewed after transformation so this variable was not used in the standardised regression-based *z*-scores.

For the mood variables, all of the mood factor change scores met the assumption of normality for both groups except the depression factor for the healthy volunteers. Therefore, paired *t* tests will be used to evaluate change for each of the mood factors except this one where the Wilcoxon sign will be used instead. For the ABNAS, all the variables did not meet the assumption for normality so the Wilcoxon sign test will be used to assess changes in self-reported cognitive complaints by the patients with epilepsy.

Measuring change

As there are various methods to assess change in cognitive functioning over time, a brief description of these methods ad justification for their use is provided below.

Factors that affect test-retest performance

Assessing cognitive change in neuropsychology is not a straightforward process. Test-retest situations are affected by a number of factors, as shown in Table 5.8, which make determining whether an observed change is a 'true' change or due to measurement error (e.g. practice effects, regression to the mean) or other factors difficult (Temkin *et al.,* 1999). Being able to determine whether a change is a 'true' change in performance is particularly important when assessing the effects of interventions, for example, outcomes after surgery or in clinical drug trials (McSweeney *et al.*, 1993, Chelune *et al.*, 1993, Hermann *et al.*, 1996, Salinsky *et al.*, 2001). In these cases, it is important to know whether the change observed is greater than that would be expected for comparable individuals who are retested over similar intervals but are not exposed to the intervention (Chelune *et al.*, 1993). Evaluating clinically meaningful change is also made more difficult because normative data on change over time for many neuropsychological measures do not exist (McSweeney *et al.,* 1993).

Over the last two decades, several statistical techniques have been developed to evaluate clinically meaningful and statistically reliable cognitive change. These correct for some of these sources of error and bias, in particular, practice effects and regression to the mean. Temkin *et al.,* (1999) and Frerichs & Tuokko (2005) have reviewed and compared these different methods of evaluating change. Two of these main methods will be described in the section below.

Table 5.8: Potential sources of bias and error in test-retest situations (adapted from Strauss et al., 2006)

	Source	Example
Bias	Intervening variables	• Events of interest (e.g. surgery, medical intervention, rehabilitation) • Extraneous events
	Practice effects	• Memory for content • Procedural learning • Other factors • Familiarity with testing context and examiner • Performance anxiety
	Demographic considerations	• Age (maturational effects and ageing) • Education • Gender • Ethnicity • Baseline ability
Error	Statistical errors	• Measurement error • Regression to the mean
	Random or uncontrolled events	• Random or uncontrolled events

Reliable change index (RCI)

The reliable change index was first developed by Jacobson & Truax (1991) as a way of evaluating outcomes from psychotherapy research. Using a comparable control group, calculating the RCI for a test measure involves dividing change scores by the standard error of the difference between the two scores. The standard error of the difference is derived from the standard error of the measurement and describes the spread of the distribution of change scores that would be expected if no actual change had occurred (Chelune *et al.*, 1993). This distribution is used to establish confidence intervals for the test measure (usually 90% CI). The 90% confidence intervals are created by multiplying the standard error of the difference by ± 1.64. This then determines two cut-off points which clinically significant change can be evaluated against. The 90% CIs are the most commonly used cut-off points, as they are the values that statistically would be expected to occur without real change only 10% of the time by chance, 5% in a positive direction and 5% in a negative direction (Chelune *et al.*, 1993). If a change score is greater than the RCI in either direction, this means that a change score of that magnitude would only have occurred in the comparable population less than 5% of the

time and is considered to be a statistically reliable change (Chelune *et al.*, 1993; Hermann *et al.*, 1996). Initially, the RCI did not correct for practice effects. However, Chelune and colleagues (1993) introduced the subtraction of a constant into the equations to correct for the effects of practice.

RCIs have been used in epilepsy research, particularly in assessing neuropsychological outcome after epilepsy surgery (Chelune *et al.*, 1993, Hermann *et al.*, 1996). The main advantages and disadvantages of using RCIs are summarised in Table 5.9.

Table 5.9: Advantages and disadvantages of using RCIs

Advantages	Disadvantages
• They allow clinicians to determine whether an individual has shown statistically meaningful decline by providing information on how large a change needs to be to be considered statistically meaningful (Chelune *et al.*, 1993)	• They do not provide information about the relative magnitude of change, only that a change has exceeded the cut-off point to be considered meaningful (Hermann *et al.*, 1996)
• They take into account the effects of practice and measurement error	• They do not allow comparisons across other measures and cognitive domains (Hermann *et al.*, 1996)
	• They do not correct for regression to the mean effects (Salinsky *et al.*, 2001, Strauss *et al.*, 2006)
	• They performed less well in predicting follow-up scores when evaluated in a large sample of neurologically normal adults (Temkin *et al.*, 1999)[7]

Standardised regression-based change scores (SRBs)

Standardised regression-based change scores are an alternative and complementary method to the reliable change index. They were first developed by McSweeney *et al.*, (1993) to assess outcomes following epilepsy surgery. Using a comparable control group, linear

[7] However, Frerichs & Tuokko (2005) found that RCIs were the most accurate method for defining normal change in a sample of older adults, aged over 65 years, followed-up as part of the population-based Canadian Study of Health and Ageing.

regression techniques are employed to create regression equations that predict retest performance using baseline test scores as the predictor variable (simple regression) (McSweeney *et al.*, 1993). Other factors that might also affect follow-up test performance can be included in the regression model (multiple regression). These can include: age; gender; education; race; duration of illness; age of onset; test-retest interval; a measure of general intellectual function or overall neuropsychological competence at baseline (Hermann *et al.*, 1996, 2006b, Temkin *et al.*, 1999, Salinsky *et al.*, 2001, Martin *et al.*, 2002, Duff *et al.*, 2005, Frerichs & Tuokko *et al.*, 2005, Martin *et al.*, 2006). However, baseline score is the most important predictor of follow-up score (McSweeney *et al.*, 1993, Hermann *et al.*, 1996, Temkin *et al.*, 1999; Martin *et al.*, 2002, 2006, Duff *et al.*, 2005).

The regression equations derived from the comparable control group are then applied to the individual or group of interest. These generate predicted scores that are compared with the observed scores. The difference between the observed and predicted scores can then be converted to standardised *T* scores (M=50, SD=10) (McSweeney *et al.*, 1993) or *z*-scores (M=0, SD=1) (Hermann *et al.*, 1996) by dividing the difference by the standard error of the estimate of the regression equation. Similar to the RCIs, cut-off values can be calculated to determine statistically reliable change (e.g. $p<.05$). For example, an SRB $\geq\pm1.64$ means that a change score of that magnitude would only have occurred in the comparable population less than 5% of the time (Martin *et al.*, 2002).

SRB change scores have been used in studies involving people with epilepsy to assess cognitive outcomes following epilepsy surgery (McSweeney *et al.*, 1993, Hermann *et al.*, 1996, Martin *et al.*, 2002); the cognitive side effects of antiepileptic drug treatment (Salinsky *et al.*, 2002, 2004, 2005); cognitive change in patients with chronic temporal lobe epilepsy (Hermann *et al.*, 2006b) and to evaluate change scores on a health-related quality of life instrument (Martin *et al.*, 2006). They have also been used to develop regression equations for a battery of tests for use in community-dwelling older adults (Duff *et al.*, 2005). The advantages and disadvantages of using SRB change scores are summarised in Table 5.10.

Table 5.10: Advantages and disadvantages of using SRB change scores

Advantages[β]	Disadvantages
• They put all changes on a common metric so the relative change across measures and cognitive domains can be compared	• Less accurate for those individuals whose baseline neuropsychological test scores are at the extremes (Duff *et al.*, 2005)
• They can be plotted on graphs to provide visual profiles of cognitive change relative to a comparison control group	
• They take into account practice effects and regression to the mean, as well as other factors that affect test-retest performance (e.g. baseline performance, age, sex and education)	
• They provide information about expected change, which can be compared to observed change	
• Multiple regression techniques were considered to be the most accurate at predicting follow-up scores in a large sample of neurologically normal adults (Temkin *et al.*, 1999)	

[β] These are summarised from McSweeney *et al.*, 1993, Hermann *et al.*, 1996, 2006b, Temkin *et al.*, 1999, Salinsky *et al.*, 2001, Martin *et al.*, 2002

For this 12 month analysis, SRB change scores were chosen to evaluate cognitive change for several reasons, described in Table 5.11. The test-retest scores for the healthy volunteers were used to create the regression equations, using the method by McSweeney *et al.*, (1993) described above. The regression equations involved regressing baseline scores, age, sex and education on 12 month scores (see Table C.2). Age in years was entered as a continuous variable, sex as a dichotomous variable (0=female, 1=male) and education was divided into three categories (low ≤11yrs, medium 12-15yrs or high >15 yrs). Two dummy variables were created so that education could be entered into the regression. These regression equations were then applied to the patients with epilepsy to predict their test performance at 12 months. The difference between predicted and observed scores was calculated and divided by the standard error of the estimate of the regression equation to obtain standardised *z*-scores. The standardised *z*-scores were transformed by multiplying the timed tasks by minus one, so that higher scores on all tasks reflected better performance (Temkin *et al.*, 1999). Dependent *t* tests were undertaken to see if there were significant differences between the observed and predicted 12 month scores.

Table 5.11: Reasons for using SRB change score techniques in this research

Reason	Importance in this research
Takes into account other factors	• In order to ascertain the impact of epilepsy and its treatment, need to adjust for other potentially confounding effects
Expected vs observed change	• PWE vs. healthy controls have retest performances that are characterised by a lack of a practice effect (Hermann *et al.*, 2006b). Comparisons of baseline and retest scores only looking at measures of central tendency (e.g. paired *t* tests) can lead to misinterpretation of data because practice effects are not taken into account (Chelune *et al.*, 1993) • No change in performance may be interpreted as stable performance when a lack of a practice effect might actually reflect a decline in performance (Martin *et al.*, 2002)
Common metric	• Useful to see if particular cognitive domains were vulnerable to the effects of epilepsy and its treatment over the first 12 months
Individual analysis	• Identify those patients who exhibit clinically significant changes and explore their characteristics (Hermann *et al.*, 2006)
Continuous measure	• Able to evaluate potential demographic and clinical factors associated with cognitive decline
Replication	• Several similar studies have used these statistical techniques to investigate change in people with epilepsy (Salinsky *et al.*, 2001, 2002, 2005, Hermann *et al.*, 2006b)

Investigating relationships

Spearman's correlations were carried out to investigate relationships between regression-based *z*-scores and the number of seizures and the number of tonic-clonic seizures since baseline. Differences in the standardised regression based *z*-scores between those who were or were not seizure free for the 12 month period were assessed by independent *t* tests. One way ANOVAs were undertaken to investigate differences between those with partial, generalised and unclassified epilepsy. Pearson correlations were undertaken to assess relationship between change scores and mood.

Individual level analysis

As described in section 5.5.2 ('Individual-level analysis'), an impairment index was created, which represents the proportion of test scores that were classified as abnormal (Oyegbile *et al.*, 2004, Hermann *et al.*, 2006b, 2007a). Abnormal test performance was defined as a SRB *z*-score ≤-2.0. This criterion for abnormal test performance has been used in other similar

studies (Hermann *et al.*, 2006b). Exploratory analyses (using independent *t*, Mann Whitney and chi square tests) were conducted to identify the characteristics of those who were classified as having abnormal test performance.

5.5.4 Statistical analysis for chapter 8

Demographic and clinical characteristics

Descriptive statistics were used to describe the demographic and clinical characteristics of the patients who took part in this follow-up study. As consent to access medical records had not been given by refusers or non-responders, differences in current demographic and clinical characteristics between patients who took part and those that did not could not be evaluated. However, differences in baseline demographic and clinical characteristics and neuropsychological test scores at baseline and 12 months could be compared.

Independent *t* tests and chi square analysis were undertaken to investigate possible differences between those who agreed to participate and those who did not in terms of their demographic, clinical and neuropsychological characteristics. However, for some of the clinical variables (e.g. previous/current neurological disorders) several cells in the contingency tables had expected counts of less than five, so chi square tests were not undertaken for these variables. Instead, descriptive statistics were provided.

Neuropsychological and psychological test data

Assessing the spread of the data

The differences between baseline and follow-up neuropsychological test scores were assessed to see whether they met the assumption of normality. The spread of the differences were assessed by visually inspecting histograms, Q-Q plots, the values of skewness and kurtosis and the results of the Kolmogorov-Smirnov test.

For the neuropsychological test variables, thirteen of the difference scores did not differ from the normal distribution and so parametric analyses (dependent *t* tests) were carried out on these. However, differences for BCRT, simultaneous recognition of words and the delayed

subtest of the RAVLT differed significantly from the normal distribution and so non-parametric analyses (Wilcoxon signed-rank test) were used for these measures. The scores for the Stroop colour-word task were negatively skewed due to low ceiling effects, and the difference scores were also skewed, so this variable was again converted to a categorical one based on normative data (see section 5.5.2).

For the mood variables, the difference scores for each mood factor did not differ from the normal distribution and so parametric analyses (dependent *t* tests) were used to assess change in these measures. For the ABNAS, half the sub-domains (fatigue, motor and language) differed from the normal distribution and half did not (memory, concentration, slowing). To maintain consistency within the ABNAS, non-parametric (Wilcoxon signed-rank tests) were used to assess differences between self-reported cognitive complaints at baseline and follow-up for all sub-domains.

Percentage change scores

A discussed in section 5.5.3 above ('Measuring change'), several statistical methods have been developed to evaluate reliable cognitive change. However, for this part of the thesis, reliable change indices or standardised regression-based change scores could not be applied because the control group had not been evaluated over the same test-retest interval (range 3.5-7 years). As baseline score is the most important predictor of follow-up score (McSweeney *et al.*, 1993, Hermann *et al.*, 1996; Temkin *et al.*, 1999, Martin *et al.*, 2002, 2006, Duff *et al.*, 2005), percentage change scores were calculated instead that take into account the individual's baseline score. These were calculated by: [*(follow-up score-baseline score)/baseline score]*100*. These percentage change scores were transformed for timed tasks so that for all tests positive values indicated improvement from baseline and negative values indicated decline from baseline (Temkin *et al.*, 1999).

The spread of the percentage change scores were also investigated by inspecting histograms, Q-Q plots, values of skewness and kurtosis and the results of the Kolmogorov -Smirnov test. The percentage change scores differed from the normal distribution and so non-parametric analyses were carried out on these variables.

Factors associated with cognitive change

Several demographic, clinical and psychological factors were identified that might influence cognitive change, based on the literature described in Chapter 3 and Chapter 4. Their relationship with percentage change scores were assessed through separate univariable analyses. These independent variables were either analysed as continuous variables or transformed into dichotomous ones. The independent variables were: seizure freedom for at least the previous 12 months (yes/no); age; years of education; duration of epilepsy; presence of co-morbidities at follow-up (yes/no); tension factor of the POMS; prior neurological deficit or abnormal imaging at baseline (yes/no).

Seizure type was not analysed due to the small numbers of patients who were classified as having generalised or unclassified seizures. Relationships between percentage change scores and these demographic, clinical and psychological factors were explored through Spearman correlations, Mann Whitney and Kruskal-Wallis tests.

Individual cognitive change

To assess cognitive change at an individual-level and evaluate the clinical significance of results, the proportion of patients who had experienced cognitive decline was calculated. This was calculated relative to the cross-sectional standard deviation of the relevant baseline scores (*follow-up score-baseline score/ SD of the baseline score*) (Aldenkamp *et al.*, 2000, Frerichs & Tuokko, 2005, Gomer *et al.*, 2007). Cognitive decline was defined in two ways: as a decline of more than or equal to 1.5SD or 2SD in performance on any of the neuropsychological tests.

Some studies have used less conservative values of ≥1SD to define decline (e.g. Gomer *et al.*, 2007). However, several previous studies have also defined cognitive decline using the more conservative values above (e.g. Andersson-Roswall *et al.*, 2004). The more conservative values were chosen so as not over-estimate the number of patients who were classified as experiencing cognitive decline, especially as evaluating change using this standard deviation method has been found to over-classify deterioration in test performance

compared with other methods (e.g. RCIs and regression-based models) (Frerichs & Tuokko, 2005).

An exploratory analysis was conducted to identify the demographic and clinical characteristics of those who were identified as having cognitive decline (defined using the more conservative criterion of ≥2SD). Independent *t*, Mann Whitney and chi square tests were undertaken to assess differences between those characterised as having or not having cognitive decline. However, where more than two cells in the contingency tables had expected counts of less than five, only descriptive statistics were provided.

5.5.5 Reporting of statistics

Throughout all the results chapters, for each inferential test, differences in means and medians are reported along with 95% confidence intervals and corresponding *p*-values. The 95% confidence intervals for differences in medians are not provided in SPSS so were calculated using Stats Direct. For independent *t* tests, Levene's test was carried out to test for equality of variance. The *p*-values reported are the corrected values, when equality of variance was not assumed.

5.5.6 Significance level

The significance level for the inferential statistics was set at $p<.01$. This was to reduce the likelihood of making a Type I error due to the number of multiple comparisons being made. A Bonferroni correction could have been applied but due to the number of inferential tests conducted this would have been too conservative a value and would have increased the likelihood of making a Type II error.

5.6 Summary

The SANAD Neuropsychology study, as part of the SANAD trial, provided a *unique* opportunity to investigate the natural history of cognitive impairment in a sample of previously untreated patients with newly diagnosed epilepsy. Patients were assessed using a comprehensive, sensitive neuropsychological test battery before the start of antiepileptic drug

treatment and were re-assessed after three and 12 months. The recruitment of a healthy volunteer reference control group meant the performance of people with epilepsy at the time of diagnosis could be compared with people from the general population and evaluated against 'normal' test-retest performance after 12 months of AED treatment. The follow-up study provided an opportunity to study the cognitive effects of epilepsy and its treatment, without the effects of surgical intervention, three to eight years after diagnosis.

The results will be divided into three chapters and the next chapter will present the results of the comparison between patients with newly diagnosed epilepsy and healthy volunteers at the baseline assessment.

Chapter 6 Results: The immediate impact

6.1 Overview of chapter

This chapter documents and compares the cognitive profile of healthy volunteers with newly diagnosed patients with epilepsy and no known cerebral pathology, before the administration of antiepileptic drug medication. These results have formed the basis of a peer-reviewed publication by Taylor and colleagues (2009) (see Appendix D).

This chapter will describe the number of patients and healthy volunteers that were recruited and eligible for the SANAD Neuropsychology study and this analysis. Their demographic and clinical characteristics will be reported. The neuropsychological test scores of the patients with epilepsy and healthy volunteers will be compared and the impact of epilepsy, seizure and mood-related variables on cognitive functioning will be assessed. The characteristics of those who already demonstrate cognitive impairment at baseline will be explored. Finally, the relationship between subjective report of cognitive problems and objective test performance will be investigated.

6.2 Participants

6.2.1 Patients with epilepsy

A total of 257 patients with newly diagnosed epilepsy were initially recruited and assessed at baseline. The median time interval between baseline assessment and randomisation was 0 days (range 0-19 days). Three patients were excluded because later investigations found that they did not have a diagnosis of epilepsy and one was excluded because they had a learning disability. A further 31 patients were removed prior to analysis because they were found to have been previously treated with antiepileptic drugs. Therefore, 222 patients were eligible for the SANAD Neuropsychology study at baseline. Table 6.1 illustrates the number of patients recruited, assessed and were eligible from each centre.

Table 6.1: Numbers recruited, eligible and assessed at each centre

Centre	Recruited (n, %)	Eligible (n, %)
Walton Centre for Neurology & Neurosurgery, Liverpool	63 (24.5)	58 (26.1)
Royal Bolton Hospital, Bolton	53 (20.6)	45 (20.3)
University Hospital of Wales, Cardiff	49 (19.1)	45 (20.3)
Wrexham Maelor Hospital, Wrexham	27 (10.5)	20 (9.0)
Royal Hallamshire Hospital, Sheffield	21 (8.2)	17 (7.6)
Glan Clwyd Hospital, Bodelwyddan	16 (6.2)	13 (5.9)
Hope Hospital, Salford	15 (5.8)	13 (5.9)
Doncaster Royal Infirmary, Doncaster	8 (3.1)	7 (3.2)
Leigh Infirmary, Leigh	3 (1.2)	3 (1.2)
Whiston Hospital, Prescot	1 (0.4)	1 (0.5)
Royal Victoria Infirmary, Newcastle upon Tyne	1 (0.4)	0 (0.0)
Total	**257**	**222**

Thirty-eight patients had a previous or current neurological disorder, as can be seen in Table 6.2. Some patients had more than one prior neurological disorder.

Table 6.2: Previous or current neurological disorders

History	N
Neurological deficit	9
Stroke/Cerebrovascular	10
Intracranial surgery	3
Head injury	6
Meningitis/encephalitis	3
Other	17

EEGs and clinical CT/MRIs were carried out for 204 (91.9%) patients. Of those who had EEGs, EEGs were normal for 102 (50.0%) and abnormalities were found for 89 (43.6%) patients. There were no EEG reports for 13 (6.4%) patients. As shown in Table 6.3, of those with abnormal EEGs, 34 (38.2%) had a non-specific abnormality; 21 (23.6%) had a generalised abnormality and 34 (38.2%) had a focal abnormality. Scans were normal for 136 (66.7%) and abnormalities were found for 49 (24.0%) patients. There were no scan reports for 19 (9.3%) patients. The specific abnormalities were only recorded for two patients and these were white matter abnormalities and a cavernoma.

Table 6.3: EEG and imaging results

EEG/imaging abnormalities	N (%)
Non-specific abnormality	34 (38.2%)
Generalised abnormality	
Slow wave activity with spiking	13 (14.6%)
Slow wave activity without spiking	8 (9.0%)
Focal abnormality	
Paroxysmal slow activity with spiking	22 (24.7%)
Paroxysmal slow activity without spiking	12 (13.5%)
CT/MRI	
Abnormal scan	49 (24.0%)

A total of 67 patients had either a previous or current neurological history and/or abnormal neuroimaging on clinical CT or MRI. As this part of the thesis is interested in the impact of seizures and epilepsy and not the impact of a specific structural lesion or prior neurological condition, these patients were excluded from this analysis but not from the 12 month or follow-up analysis. Therefore, this analysis focuses on 155 untreated patients with newly diagnosed epilepsy who are otherwise 'neurologically' normal on the basis of the available evidence.

6.2.2 Healthy volunteers

A total of 90 healthy volunteers from the general population were recruited into the Neuropsychology study to act as a non-epilepsy control group. Three healthy volunteers were excluded from the study. One because they disclosed a severe head injury as a child; one withdrew consent part way through the assessment; and the FePsy computer program crashed during one assessment and the participant was not able to arrange a convenient time to complete the assessment. Therefore, 87 healthy volunteers were eligible at baseline.

6.3 Demographic and clinical characteristics

Table 6.4 summarises the demographic characteristics of the two groups at baseline. There were no differences in sex ($\chi^2(1)=0.01$, $p=.910$) or age ($t(160.09)=-0.05$, $p=.962$) between the two groups. The mean age of the patients with epilepsy was 35.04 years (±14.41), ranging from 15-78 years and the healthy volunteers had a mean age of 35.14years (±16.37), ranging from 15-80 years. The healthy volunteers had significantly more years of education than the

patients with epilepsy ($\chi^2(2)=33.44$, $p<.001$). A higher proportion of the healthy volunteers (40.2%) had more than 15 years of education, compared with 14.2% of the patients with epilepsy. A higher proportion of patients with epilepsy (57.4%) had 11 years or less of education compared with 21.8% of healthy volunteers.

Table 6.4: Demographic characteristics of patients with epilepsy and healthy volunteers

Characteristics	PWE (n=155)	Controls (n=87)	Diff (95%CI)	*p*-value
Sex (n, %)				
Male	79 (51.0)	45 (51.7)	-0.7 (-13.7, 12.3)	.910
Female	76 (49.0)	42 (48.3)	0.7 (-12.3, 13.7)	
Mean age, yrs (SD, range)	35.04 (14.41, 15-78)	35.14 (16.37, 15-80)	-0.10 (-4.3, 4.1)	.962
Education, yrs (n, %)				
≤11	89 (57.4)	19 (21.8)	35.6 (23.2, 46.5)	<.001***
12-15	44 (28.4)	33 (37.9)	-9.5 (-22.1, 2..6)	
>15	22 (14.2)	35 (40.2)	-26.0 (-37.7, -14.6)	

*$p<.05$, **$p<.01$, ***$p<.001$

As shown in Table 6.5, on average patients with epilepsy experienced nine seizures before randomisation to SANAD. There were six patients (3.9%) whose number of seizures before randomisation could be considered outliers but despite their number of seizures being in the thousands, they had never been treated with antiepileptic drugs previously. Unfortunately, as part of the recruitment process, the reasons why they had never previously sought treatment were not recorded. Possible reasons were that they had ignored or misinterpreted their symptoms or were unaware of them (Sander, 2003). This is plausible as the majority of their prior seizures included myoclonic seizures, typical absences and simple or complex partial seizures, which may have gone undetected. Seizure unawareness, particularly of partial seizures is common, as patients are often dependent on signs such as muscle pain, tongue biting and reactions of others to become aware that a seizure has occurred (Hoppe *et al.*, 2007). Only one patient had experienced 300 tonic-clonic seizures, which had not previously been treated. Alternatively, they may not have wanted to take AEDs because of concerns about the harmful effects of treatment and its role as a 'stigma cue' (Scambler, 1989, Jacoby *et al.*, 2007).

The majority of people with epilepsy (70.3%) had experienced partial seizures, 15.5% had experienced generalised seizures and 14.2% had experienced tonic-clonic seizures that could not be classified as either primary or secondarily generalised. The mean age of first seizure was 29.90 years (±15.68), ranging from 2-76 years. The median length of time between first seizure and randomisation was 597 days (25^{th}-75^{th} centiles 188-1953). A small proportion (3.9%) had previously had febrile convulsions and 10.3% had a familial history of epilepsy.

Table 6.5: Clinical characteristics of the patients with epilepsy

Clinical characteristics	
History of seizures, n (%)	
Febrile convulsions	6 (3.9)
Any other acute symptomatic seizures	1 (0.6)
Epilepsy in 1st degree relatives, n (%)	16 (10.3)
Median no of seizures (25^{th}-75^{th} %iles)	9 (3-100)
Mean age at first seizure, yrs (SD, range)	29.90 (15.68, 2-76)
Median interval between 1st seizure and rand, days (25-75^{th} %iles)	597 (188-1953)
Classification of seizures (n, %)	
Partial	
Simple partial	6 (3.9)
Complex partial	25 (16.1)
Simple or complex with secondarily generalised tonic-clonic	33 (21.3)
Combination of partial-onset seizures	45 (29.0)
Generalised	
Typical absence	1 (0.6)
Tonic-clonic	11 (7.1)
Combination of generalised-onset seizures	12 (7.7)
Unclassified	
Tonic-clonic (uncertain whether or not secondarily generalised)	22 (14.2)

As shown in Table 6.6, the majority of patients (69.7%) were classified as having symptomatic/cryptogenic partial epilepsy; 14.8% were classified as having idiopathic generalised epilepsy and 14.2% were classified as having unclassified epilepsy. One patient was classified as having idiopathic partial epilepsy (0.6%) and one (0.6%) was classified as having photosensitive epilepsy.

Table 6.6: Epilepsy syndrome

	N (%)
Idiopathic partial	
Childhood epilepsy with occipital paroxysms	1 (0.6)
Symptomatic/cryptogenic partial	
Temporal lobe	38 (24.5)
Frontal lobe	1 (0.6)
Parietal lobe	2 (1.3)
Occipital lobe	2 (1.3)
Partial epilepsy localisation not specified	65 (41.9)
Idiopathic generalised	
Juvenile absence	2 (1.3)
Juvenile myoclonic	10 (6.5)
Epilepsy with tonic-clonic seizures on awakening	2 (1.3)
Other idiopathic generalised epilepsy not specified	9 (5.8)
Other syndrome	1 (0.6)
Unclassified	22 (14.2)

6.4 Differences at baseline

6.4.1 Neuropsychological test raw scores

Table 6.7 compares the performance of patients with epilepsy and healthy volunteers across the neuropsychological test battery at baseline. Looking at the raw scores, patients performed worse than healthy volunteers on 13/16 cognitive measures and this reached statistical significance for 10/16 measures. Patients demonstrated significantly worse performance on the finger tapping task using both dominant ($t(210.54)=-3.75$, $p<.001$) and non-dominant hand ($t(223)=-2.99$, $p=.003$). They performed more poorly on the information processing ($t(240)=-3.78$, $p<0.001$) and motor speed ($t(218.90)=-4.45$, $p<.001$) tasks of the Adult Memory and Information Processing Battery. They recalled fewer story units both immediately ($t(240)=-5.47$, $p<.001$) and after a delay ($t(240)=-5.31$, $p<.001$) on a story recall task. They recalled fewer words immediately ($t(240)=-4.27$, $p<.001$) and after a delay ($t(240)=-3.54$, $p<.001$) on the Rey Auditory Verbal Learning Task. They performed more poorly on the serial recognition of figures task ($t(234)=-4.36$, $p<.001$) and generated fewer words on the verbal fluency test ($t(240)=-5.03$, $p<.001$). There was a trend for patients with epilepsy to respond more quickly than healthy volunteers on the visual reaction time task with the non-dominant hand ($t(229)=-$

2.31, p=.022) but respond more slowly on the computerised visual search task (t(235)=1.75, p=.082).

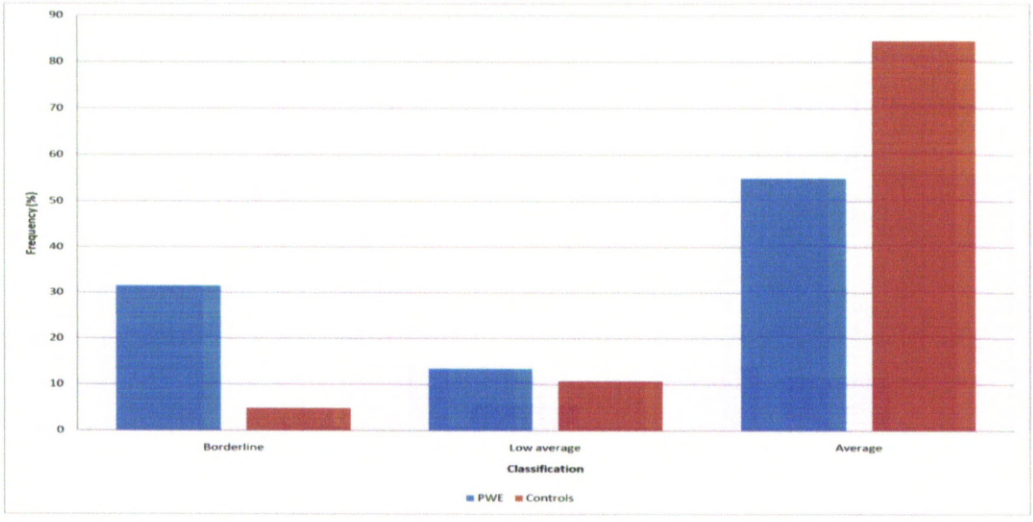
Table 6.7: Baseline performance of patients with epilepsy and healthy volunteers

Variable	PWE	Controls	Diff (95% CI)	p-value
Finger Tapping				
Dominant	57.11 (9.25, 144)	61.10 (6.61, 81)	-3.99 (-6.09, -1.89)	<.001***
Non-dominant	52.03 (7.87, 144)	55.02 (5.86, 81)	-2.99 (-4.97, -1.02)	.003**
Log Visual RT (ms) †				
Dominant	5.71 (0.22, 143)	5.72 (0.14, 87)	-0.01 (-0.06, 0.03)	.563
Non-dominant	5.69 (0.18, 144)	5.74 (0.15, 87)	-0.05 (-0.10, -0.01)	.022*
Binary Choice RT (ms) †	354 (306-426, 147)	359 (318.75-410, 86)	0.00 (-19.00, 20.00)	.986
Log CVST (s) †	2.34 (0.29, 151)	2.27 (0.29, 86)	0.07 (-0.01, 0.15)	.082
Word recog				
Serial	15.39 (4.11, 152)	16.10 (3.76, 87)	-0.71 (-1.76, 0.35)	.187
Simultaneous	20.00 (18.00-22.00, 152)	21.00 (18.00-22.00, 84)	-1.00 (-1.00, 0.00)	.157
Figure recog				
Serial	14.42 (3.85, 149)	16.73 (4.08, 87)	-2.31 (-3.36, -1.27)	<.001***
Story recall				
Immediate	7.69 (2.92, 155)	9.92 (3.26, 87)	-2.23 (-3.04, -1.43)	<.001***
Delayed	6.78 (3.06, 155)	9.02 (3.31, 87)	-2.24 (-3.07, -1.41)	<.001***
Rey AVLT				
Immediate	45.17 (9.66, 155)	50.70 (9.66, 87)	-5.53 (-8.08, -2.98)	<.001***
Delayed	8.80 (3.33, 155)	10.37 (3.28, 87)	-1.57 (-2.44, -0.69)	<.001***
Verbal fluency	34.15 (11.58, 155)	41.75 (10.70, 87)	-7.59 (-10.57, -4.62)	<.001***
AMIPB				
Info Processing	60.15 (15.89, 155)	68.17 (15.69, 87)	-8.02 (-12.19, -3.84)	<.001***
Motor speed	46.44 (9.85, 152)	51.86 (7.47, 87)	-5.42 (-7.65, -3.19)	<.001***

Values reported are means and SD or medians and 25th-75th centiles, † higher score means worse performance, *p<0.05, **p<.01, ***p<.001

Figure 6.1 compares the performance of patients with epilepsy and healthy volunteers on the Stroop Neuropsychological Screening Test, after adjusting for age. Significantly more patients with epilepsy (31.5%) than healthy volunteers (4.8%) fell in the borderline ranges and significantly fewer patients with epilepsy (55.0%) compared with healthy volunteers (84.5%) fell in the average ranges (χ^2(2)=25.03, p<.001)

Figure 6.1: Performance of patients with epilepsy and healthy volunteers on the Stroop colour-word task



6.4.2 Age, sex and education adjusted *z*-scores

Table 6.8 compares the age, sex and education adjusted *z*-scores of patients with epilepsy and healthy volunteers across the neuropsychological test battery. After adjusting for sex, age and education, there were statistically significant differences on 6/14 measures. Patients demonstrated significantly worse performance on the finger tapping task with the dominant hand ($t(209.77)=-4.10$, $p<.001$). They performed more poorly on the motor speed task of the Adult Memory and Information Processing Battery ($t(232.88)=-3.49$, $p<.001$). They recognised fewer figures on the serial recognition task ($t(234)=-5.78$, $p<.001$). They recalled fewer words immediately ($t(240)=-5.65$, $p<.001$) and after a delay ($t(240)=-4.29$, $p<.001$) on the Rey Auditory Verbal Learning Task. They also recalled significantly fewer units of a story recall task immediately ($t(240)=-2.59$, $p=.010$) and there was a trends for patients with epilepsy to recall fewer story units after a delay ($t(240)=-2.28$, $p=.024$).

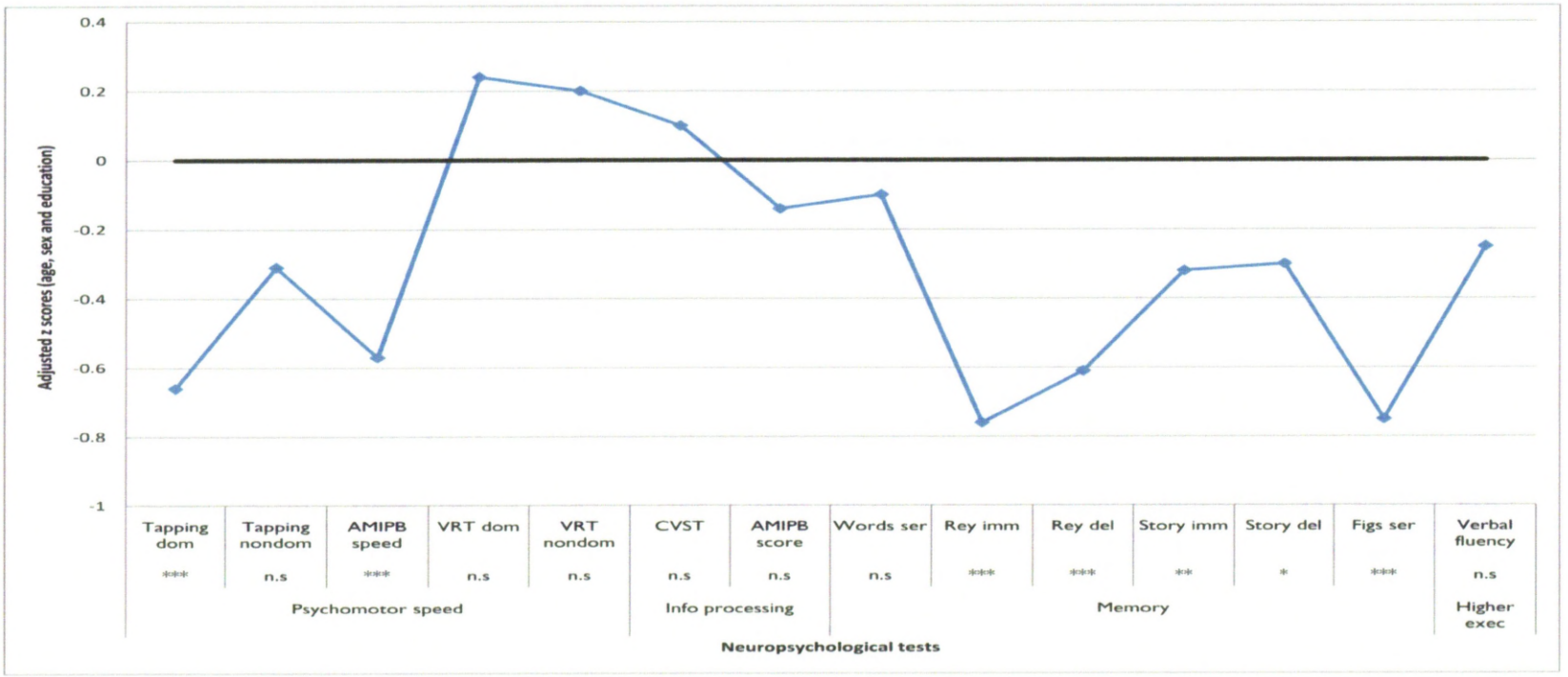
Table 6.8: Performance of patients with epilepsy compared with healthy volunteers (age, sex and education adjusted z-scores)

Variable	PWE (mean, SD, n)	Controls (mean, SD, n)	Diff (95% CI)	*p*-value
Finger Tapping				
Dominant	-0.66 (1.39, 144)	0.00 (1.00, 81)	-0.66 (-0.97, -0.34)	<0.001***
Non-dominant	-0.31 (1.33, 144)	0.00 (1.00, 81)	-0.31 (-0.64, 0.03)	0.070
Log Visual RT (ms)				
Dominant	0.24 (1.65, 143)	0.00 (1.00, 87)	0.24 (-0.11, 0.58)	0.177
Non-dominant	0.20 (1.21, 144)	0.00 (1.00, 87)	0.20 (-0.09, 0.49)	0.171
Log CVST (s)	0.10 (1.05, 151)	0.00 (1.00, 86)	0.10 (-0.17, 0.38)	0.457
Word recognition				
Serial	-0.10 (1.12, 152)	0.00 (1.00, 87)	-0.10 (-0.38, 0.19)	0.495
Figure recognition				
Serial	-0.75 (0.94, 149)	0.00 (1.00, 87)	-0.75 (-1.01, -0.50)	<0.001***
Story recall				
Immediate	-0.32 (0.90, 155)	0.00 (1.00, 87)	-0.32 (-0.57, -0.08)	0.010**
Delayed	-0.30 (0.97, 155)	0.00 (1.00, 87)	-0.30 (-0.56, -0.04)	0.024*
Rey AVLT				
Immediate	-0.76 (1.01, 155)	0.00 (1.00, 87)	-0.76 (-1.03, -0.50)	<0.001***
Delayed	-0.61 (1.09, 155)	0.00 (1.00, 87)	-0.61 (-0.89, -0.33)	<0.001***
Verbal fluency	-0.25 (1.06, 155)	0.00 (1.00, 87)	-0.25 (-0.52, 0.03)	0.079
AMIPB				
Info Processing	-0.14(1.08, 155)	0.00 (1.00, 87)	-0.14 (-0.42, 0.14)	0.322
Psychomotor speed	-0.57 (1.53, 152)	0.00 (1.00, 87)	-0.57 (-0.90, -0.25)	<0.001***

p<.05, ** *p*<.01, ***p<.001

Figure 6.2 illustrates the neuropsychological test performance of patients with epilepsy compared with healthy volunteers, with the x-axis representing the control mean. After correcting for age, sex and education, patients with epilepsy performed worse than healthy volunteers across the majority of measures. However, patients with epilepsy performed better than the healthy volunteers on a visual reaction time task with both the dominant ($t(228)=1.35$, $p=0.177$) and non-dominant hand ($t(207.27)=1.37$, $p=0.171$) and they responded more quickly on the Computerised Visual Search Task ($t(235)=0.75$, $p=0.457$) but these differences did not reach statistical significance. Memory and psychomotor speed domains were most affected, with patients demonstrating subtle dysfunction, performing between 0.5 and 1 SD below the control mean.

Figure 6.2: Mean performance of patients with epilepsy across the neuropsychological test battery relative to healthy controls (represented by the x-axis)



dom=dominant, nondom=non-dominant, ser=serial, imm=immediate, del=delayed, exec=executive

6.5 Impact of epilepsy, seizure and mood related variables

6.5.1 Impact of previous seizure activity

Despite a large proportion of patients experiencing several seizures before enrolment, Table 6.9 illustrates that there were no relationships between the total numbers of seizures or the total number of generalised tonic-clonic seizures (primary and secondarily generalised) and any of the cognitive measures. Although, there was a trend for performance on the immediate subtest of the Rey Auditory Verbal Learning Test to be associated with the total number of seizures before baseline. Serial recognition of figures was significantly associated with the time interval since first seizure. Shorter duration of epilepsy was associated with poorer performance on this task, although there were no relationships on any other measure.

Table 6.9: Relationship between no of seizures, time since first seizure and test performance

Variable	Total number of seizures	Total number of GTCS	No of days since first seizure
Finger Tapping			
Dominant	.043 (*p=.612*)	.104 (*p=.217*)	.057 (p=.499)
Non-dominant	.016 (*p=.850*)	.117 (*p=.161*)	.099 (p=.239)
Log Visual RT (ms)			
Dominant	.102 (*p=.224*)	-.013 (*p=.878*)	.116 (p=.169)
Non-dominant	.031 (*p=.716*)	-.042 (*p=.618*)	.046 (p=.584)
Log CVST (s)	.076 (*p=.351*)	.018 (*p=.826*)	.125 (p=.126)
Word recognition			
Serial	.066 (*p=.420*)	.026 (*p=.749*)	.151 (p=.063)
Figure recognition			
Serial	.031(*p=.711*)	.084 (*p=.309*)	.212 (p=.010)**
Story recall			
Immediate	.112 (*p=.167*)	-.013(*p=.874*)	.015 (p=.855)
Delayed	.129 (*p=.111*)	.086 (*p=.289*)	.054 (p=.506)
Rey AVLT			
Immediate	.180 (*p=.025*)*	-.058 (*p=.472*)	.099 (p=.218)
Delayed	.031(*p=.701*)	.031 (*p=.706*)	.049 (p=.543)
Verbal fluency	.031(*p=.700*)	-.023 (*p=.778*)	.105 (p=.195)
AMIPB			
Info Processing	0.106 (*p=.189*)	-0.109 (*p=.176*)	.123 (p=.128)
Psychomotor	0.002 (*p=.976*)	-0.050 (*p=.543*)	.006 (p=.944)

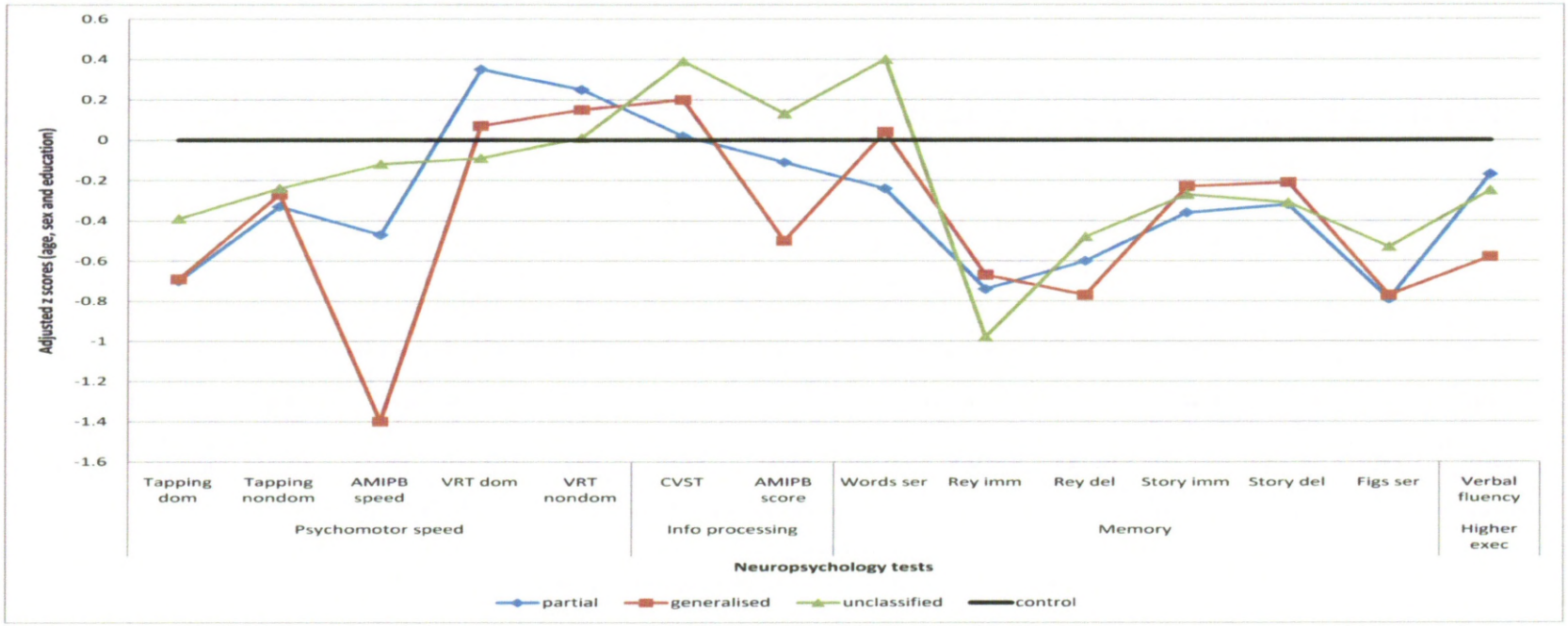
Values reported are Spearman's rho correlation coefficient and *p*-values, *$p<.05$, **$p<.01$, ***$p<.001$

6.5.2 Impact of epilepsy type

The numbers were too small to look at the cognitive profiles of each epilepsy syndrome. Instead, patients were classified into those with partial (n=109), generalised (n=24) and unclassified (n=22) epilepsy. Figure 6.3 plots the performance of the different epilepsy types, with the x-axis representing the control mean. The pattern of performance is similar across the three epilepsy groups.

When one-way ANOVAs were conducted (see Table 6.10), the only task that had significant differences between the epilepsy groups was the motor speed task of the Adult Memory and Information Processing Battery. Those with generalised epilepsy performed significantly worse than those with partial and unclassified epilepsy. Significant differences were found on four other tasks but Tukey post hoc tests revealed the differences were between patients and healthy volunteers and not between the three epilepsy groups. On the dominant hand finger tapping task those with partial epilepsy performed significantly worse than healthy volunteers. On the serial recognition of figures task, and the delayed Rey Auditory Verbal Learning Test, those with partial and generalised epilepsy performed significantly lower than the healthy volunteers. On the immediate part of this task, all three epilepsy groups performed significantly lower than the healthy volunteers but did not perform differently from each other. However, these results should be interpreted with caution due to the unequal numbers.

Figure 6.3: Performance of patients with partial, generalised and unclassified epilepsy across the neuropsychological test battery relative to healthy volunteers (represented by the x-axis)



dom=dominant, nondom=non-dominant, ser=serial, imm=immediate, del=delayed, exec=executive

Table 6.10: One way ANOVAs investigating differences in epilepsy type and healthy volunteers

Cognitive domain	F	*p*-value
Finger Tapping		
Dominant	5.01	.002**
Non-dominant	1.14	.334
Log Visual RT (ms)		
Dominant	1.12	.341
Non-dominant	0.85	.469
Log CVST (s)	1.04	.376
Word recognition		
Serial	2.48	.062
Figure recognition		
Serial	11.54	<.001***
Story recall		
Immediate	2.38	.071
Delayed	1.79	.149
Rey AVLT		
Immediate	11.05	<.001***
Delayed	6.40	<.001***
Verbal fluency	2.02	.111
AMIPB		
Info Processing	1.82	.145
Psychomotor speed	7.44	<.001***

*p<.05, **p<.01 ***p<.01

6.5.3 Impact of mood

Differences between patients with epilepsy and healthy volunteers

On the Profile of Mood States, as shown in Table 6.11, patients with epilepsy reported experiencing significantly more symptoms of tension (z=-3.57, p<.001), confusion (z=-3.64, p<.001) and significantly less vigour (z=-3.48, p=.001) than healthy volunteers.

As shown in Table 6.12, there were no significant relationships between the adjusted z-scores and the mood factors when each group was analysed separately. There was a trend for higher levels of tension to be associated with poorer serial recognition of figures (r_s=-1.63, p<.047). But generally, this suggests that the differences found on the neuropsychological tests are not mediated by mood disturbances.

Table 6.11: Differences in self-reported mood between patients with epilepsy and healthy volunteers

Variable	PWE (median, 25th-75th %iles, n)	Controls (median, 25th-75th %iles, n)	Diff (95% CI)	*p*-value
Vigour	43.75 (28.13-56.25, 155)	53.13 (43.75-59.38, 87)	-9.38 (-12.5, -3.13)	.001***
Tension	36.11 (22.22-58.33, 155)	25.00 (11.11-47.22, 87)	11.11 (5.56,16.66)	<.001***
Confusion	35.71 (21.43-53.57, 154)	21.43 (14.29-35.71, 87)	10.71(3.57, 14.29)	<.001***
Fatigue	35.71 (21.43-53.57, 154)	32.14 (21.43-53.57, 87)	3.57(-3.57, 7.14)	.558
Depression	15.00 (6.67-31.67, 155)	10.00 (3.33-23.33, 87)	3.33 (0, 6.67)	.042*
Anger	14.58 (8.33-28.13, 153)	14.58 (4.17-29.17, 87)	2.08 (-2.08, 4.17)	.485

*p<.05, **p<.01, ***p<0.001

Table 6.12: Relationships between neuropsychological test performance and mood

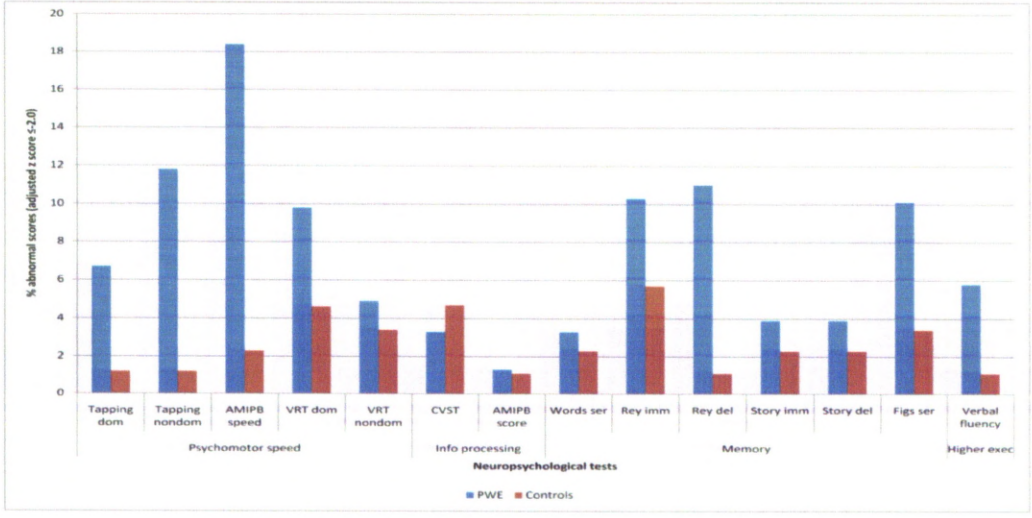
Variable	Vigour PWE	Control	Tension PWE	Control	Confusion PWE	Control
Finger Tapping						
Dominant	.038 (p=.655)	-.045 (p=.689)	-.108 (p=.198)	-.077 (p=.494)	-.159 (p=.057)	-.106 (p=.347)
Figure recognition						
Serial	-.126 (p=.125)	.010 (p=.926)	-.163 (p=.047)*	-.035 (p=.745)	-.061 (p=.458)	-.175 (p=.105)
Story recall						
Immediate	-.123 (p=.126)	.093 (p=.393)	-.062 (p=.441)	.137 (p=.206)	.039 (p=.632)	.004 (p=.970)
Rey AVLT						
Immediate	-.141 (p=.080)	-.077 (p=.478)	-.051 (p=.532)	-.036 (p=.742)	-.059 (p=.469)	-.098 (p=0.369)
Delayed	-.131 (p=.104)	-.090 (p=.408)	-.087 (p=.283)	-.037 (p=.734)	-.103 (p=.206)	.001 (p=.993)
AMIPB						
Psychomotor speed	.124 (p=.129)	-.040 (p=.716)	-.073 (p=.370)	-.165 (p=.128)	-.142 (p=.082)	-.177 (p=.101)

Values reported are Spearman's rho correlation coefficient and p values, *p<.05, **p<.01, ***p<0.001

6.6 Individual-level analysis

Figure 6.4 illustrates the percentage of patients with epilepsy and healthy volunteers who had abnormal scores for each test. A higher proportion of patients with epilepsy had abnormal test scores compared with healthy volunteers. This is particularly evident for those measures that assess memory and psychomotor speed.

Figure 6.4: Percentage of patients and healthy volunteers with abnormal scores (>2SD below the control mean) for each neuropsychological test variable



dom=dominant, nondom=non-dominant, ser=serial, imm=immediate, del=delayed, exec=executiveImpairment index

Using the impairment index, Table 6.13 compares the number of individuals who have some degree of cognitive impairment across the test battery when different criterions of abnormality were applied. When an adjusted z-score of ≤-1.5 was used as a marker of abnormality, 74.8% of the patients with epilepsy had at least one abnormal test score compared with 48.3% of the healthy volunteers. Even when the more conservative value of ≤-2.0 was used, 53.5% of the patients with epilepsy had at least one abnormal score compared with 20.7% of healthy volunteers. A higher proportion of patients with epilepsy (9.7%) had impairments on at least a quarter of the test variables compared with 2.3% of healthy volunteers. One patient had abnormal scores on more than half of the measures compared with none of the healthy volunteers.

Table 6.13: Number of patients and healthy volunteers demonstrating impairments across the test battery

	Criterion of abnormal test performance			
Proportion of tests impaired	≤-2.0		≤-1.5	
	PWE (n, %)	Controls (n, %)	PWE (n, %)	Controls (n, %)
0	72 (46.5)	69 (79.3)	39 (25.2)	45 (51.7)
≥1%	83 (53.5)	18 (20.7)	116 (74.8)	42 (48.3)
≥25%	15 (9.7)	2 (2.3)	38 (24.5)	9 (10.3)
≥50%	1 (0.6)	0 (0.0)	11 (7.1)	1 (1.1)

Using the more conservative criterion of ≤-2.0, 83 patients with epilepsy had at least one abnormal test score. These individuals were classified as being impaired. Patients were significantly more likely to be in the impaired group compared with healthy volunteers (χ2(1)=24.74, p<.001, Odds Ratio (OR) 4.42, 95%CI 2.41, 8.11). An exploratory analysis was conducted to try and identify the demographic and clinical characteristics of those patients in the impaired group. Table 6.14 presents the results of this analysis.

There were no differences between those who were classified as impaired and those who were not in terms of sex (χ^2(1)=0.05, p=.822), age at assessment (t(153)=-.03, p=.980) or education (χ^2(2)=3.30, p=.192). There were no differences between the two groups on any epilepsy-related variables. There were no differences in epilepsy type (χ^2(2)=3.73, p=.155); number of seizures at baseline (z=-1.64, p=.101) or age at first seizure (t(153)=-0.61, p=.542), although there was a trend for those with a shorter interval since their first seizure to be in the impaired group (z=-2.39, p=.017). There were no differences between the two groups on any of the mood variables.

Table 6.14: Exploratory data analysis looking at the characteristics of those classified as impaired

Variable	Impaired (n=83)	Not impaired (n=72)	Diff (95%CI)	*p*-value
Sex, n (%)				
Male	43 (51.8)	36 (50.0)	1.8 (-13.9, 17.4)	.822
Female	40 (48.2)	36 (50.0)	-1.8(-17.4, 13.9)	
Mean age, yrs (SD)	35.01 (15.05)	35.07 (13.73)	-0.06 (-4.66, 4.54)	.980
Mean age at first seizure, yrs (SD)	30.61 (16.21)	29.07 (15.12)	1.54 (-3.45, 6.54)	.542
Education, yrs (n,%)				
<11	53 (63.9)	36 (50.0)	13.9 (-1.8, 28.9)	.192
12-15	19 (22.9)	25 (34.7)	-11.8 (-26.0, 2.4)	
>15	11 (13.3)	11 (15.3)	-2.0 (-13.8, 9.2)	
Seizure type, n (%)				
Partial	53 (63.9)	56 (77.8)	-13.9 (-27.7, 0.6)	.155
Generalised	15 (18.1)	9 (12.5)	5.6 (-6.2, 17.1)	
Unclassified	15 (18.1)	7 (9.7)	8.4 (-2.9, 19.5)	
Median no of seizures (25th-75th %iles)	7 (3-98)	11 (4-100)	-2.00 (-5.00, 0.00)	.101
Median interval from 1st seizure to rand, days (25th-75th %iles)	381.00 (129-1739)	1030.50 (276-2671.75)	-234.50 (-691, -34)	.017*
Mood(median, 25th-75th %iles)				
Tension	38.89 (22.22-61.11)	34.72 (19.44-52.78)	2.78 (-2.78, 11.11)	.393
Depression	15.00 (6.67-30.00)	15.00 (5.42-31.67)	0.00 (-5.00, 5.00)	.901
Anger	14.58 (8.33-27.08)	14.58 (6.77-30.73)	0.00 (-4.17, 4.17)	.927
Vigour	43.75 (31.25-59.38)	40.63 (22.66-53.13)	6.25 (-3.13, 12.5)	.163
Fatigue	35.71 (17.86-50.00)	35.71 (21.43-59.82)	0.00 (-10.71, 7.14)	.747
Confusion	39.29 (21.43-53.57)	32.14 (21.43-56.25)	0.00 (-7.14, 7.14)	.896

*$p<.05$, **$p<.01$, ***$p<.001$

Relationship of baseline cognitive impairment with future seizure status

Table 6.15 illustrates the proportion of patients who continued to have seizures at 12 month (68.7%) and longer term follow-up (42%). Being classified as impaired at baseline was not a risk factor for active seizures at 12 months (OR=1.08, 95%CI 0.53, 2.19) or after a mean five years follow-up (OR=1.08, 95%CI 0.35, 3.36).

Table 6.15: Relationship between baseline cognitive impairment and future seizure status

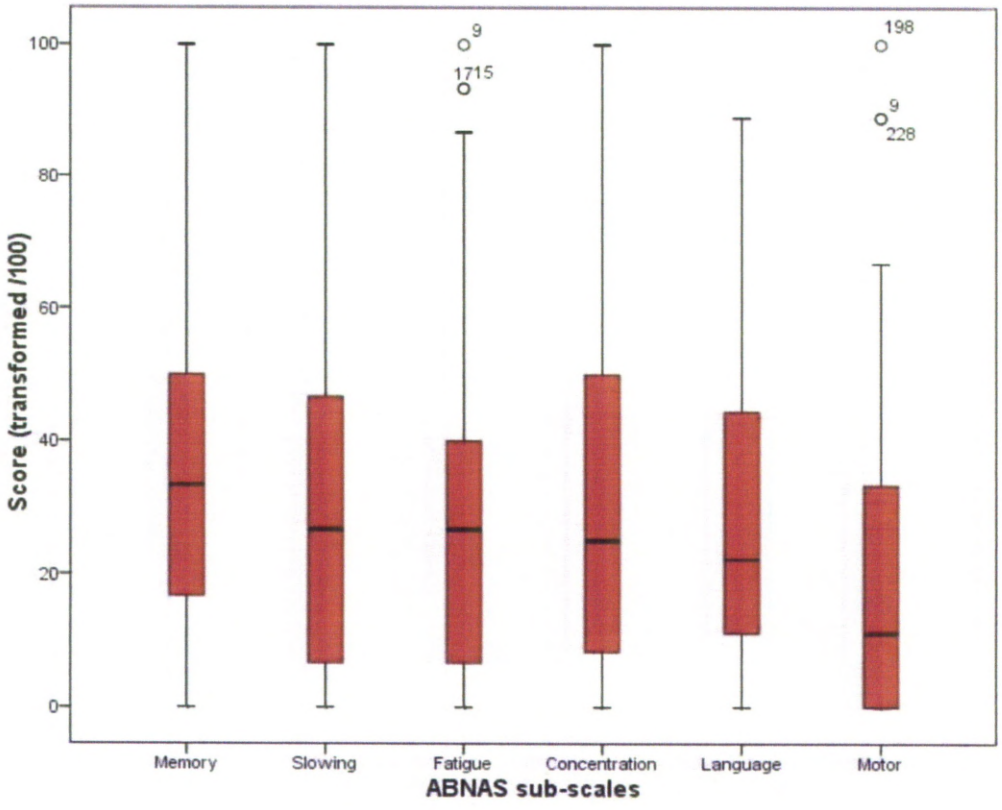
		Seizure status			
		12 months (n, %)		5 year FU (n, %)	
		Seizures	Seizure free	Seizures	Seizure free
Baseline	Impaired	59 (58.4)	26 (56.5)	12 (57.1)	16 (55.2)
	Not impaired	42 (41.6)	20 (43.5)	9 (42.9)	13 (44.8)

6.7 Subjective report of cognitive problems

6.7.1 Most commonly reported perceived cognitive problems

As shown in Figure 6.5, patients with epilepsy were already reporting problems in the areas of memory, slowing, fatigue, concentration and language before the administration of antiepileptic drug medication. The least subjective complaints were given for motor abilities.

Figure 6.5: Self-reported cognitive problems on the ABNAS



Based on their total ABNAS score, patients with epilepsy were divided into two groups: 'high scores' (≥15) or 'low scores' (<14). A cut-off of 15 was used based on the normative data for the measure (Aldenkamp *et al.*, 2002). Table 6.16 illustrates that 56.5% of the patients with epilepsy rated themselves as experiencing a high number of cognitive complaints. However, those who were classified as impaired were no more likely than those who were not impaired to report a high number of cognitive complaints (OR 0.91, 95%CI 0.48, 1.73).

Table 6.16: Relationship between ABNAS scores and impairment index

		Impairment index		Total
		Impaired	Not impaired	
ABNAS scores	Low	37 (44.6)	30 (42.3)	67 (43.5)
	High	46 (55.4)	41 (57.7)	87 (56.5)

6.8 Summary

The aim of this chapter was to document and compare the cognitive profile of newly diagnosed untreated patients with epilepsy with healthy volunteers before the administration of antiepileptic medication. A total of 155 newly diagnosed previously untreated patients with epilepsy, who were otherwise 'neurologically normal', were assessed at baseline. The majority had adult onset partial epilepsy, with a mean age of first seizure of 29.9 years. They had experienced on average nine seizures before the baseline assessment. The average duration of untreated epilepsy was one and a half years. These patients with epilepsy were compared with 87 healthy volunteers who were recruited from the general population. They were equated for age and sex; however, the healthy volunteers had significantly more years of education than the patients with epilepsy.

As a group, patients with epilepsy performed statistically significantly worse than healthy volunteers on 11/17 measures. They demonstrated significantly worse performance on the finger tapping task using both dominant and non-dominant hand. They performed more poorly on the information processing and motor speed tasks of the Adult Memory and Information Processing Battery. They recalled fewer story units both immediately and after a delay on a story recall task. They recalled fewer words immediately and after a 30 minute delay on the Rey Auditory Verbal Learning Task. They performed more poorly on the serial recognition of figures task and generated fewer words on the verbal fluency test. After adjusting for age, they made more errors on the Stroop task.

After adjusting for age, sex and education, patients performed significantly worse than healthy volunteers on 6/14 measures. They performed significantly worse on the finger tapping task with the dominant hand. They performed more poorly on the motor speed task of the Adult Memory and Information Processing Battery. They recognised fewer figures on the serial recognition task. They recalled fewer words immediately and after a delay on the Rey Auditory Verbal Learning Task. They also recalled significantly fewer units of a story recall task immediately. The domains that appeared to be most affected were memory and psychomotor speed.

The observed differences were not mediated by the type or frequency of seizure activity. There were no differences between those with partial, generalised and unclassified epilepsy, except for the motor speed task of the Adult Memory and Information Processing Battery. However, these results must be interpreted with caution due to the unequal numbers in the groups. There were no relationships between the total number of seizures or the total number of generalised tonic-clonic seizures before the baseline assessment and any of the neuropsychological test variables. The number of days since the first seizure was also not associated with neuropsychological test performance, except for the serial recognition of figures task.

There were differences between the current mood state of patients with epilepsy and healthy volunteers. Patients with epilepsy reported experiencing more mood disturbance, in particular, more symptoms of tension and confusion and less vigour than healthy volunteers. However, these mood disturbances were not related to cognitive performance except for the serial recognition of figures task.

At an individual level, patients with epilepsy had a higher proportion of abnormal scores (adjusted *z*-score ≤-2.0) across the test battery and were four times more likely than healthy volunteers to demonstrate cognitive impairment (defined as at least one abnormal test score). Fifty four percent were classified as having cognitive impairment. Epilepsy, demographic or mood variables did not explain the differences between those patients who were or were not classified as impaired, although there was a trend for those with more recent onset seizures to be in the impaired group. Being classified as impaired at baseline was not a predictor of continuing seizures at 12 months or longer term follow-up.

The most commonly reported cognitive problems on the ABNAS self-report measure were in the areas of memory and slowing, consistent with the objective findings. However, patient's subjective report of cognitive impairments did not always correspond with their objective neuropsychological test performance. Fifty eight percent of patients reported a high number of cognitive complaints, despite not experiencing abnormal cognitive performance across the test battery. The patients and healthy volunteers have been followed-up after 12 months of treatment. Chapter 7 presents the results of this analysis.

Chapter 7 Results: The shorter term impact

7.1 Overview of chapter

This chapter will compare the cognitive trajectory of healthy volunteers with patients with newly diagnosed epilepsy after the first 12 months of epilepsy treatment. The numbers of patients and healthy volunteers who were re-assessed after 12 months will be reported. The demographic and clinical characteristics of the patients and healthy volunteers will be described and changes in cognition from baseline to 12 months will be compared. The factors related to cognitive change will be investigated and exploratory analyses will be carried out to identify the characteristics of those who exhibit the most cognitive impairment.

7.2 Participants

7.2.1 Recruitment

Patients with epilepsy

A total of 147 (66.2%) patients with epilepsy were re-assessed a median 12 months after their baseline assessment (range 9-18 months). As shown in Table 7.1, patients with epilepsy dropped out of the study for several reasons including death (n=4); being lost to follow-up (n=22) and withdrawal of consent (n=14). Three withdrew due to family pressures and one withdrew due to depression. Reasons for withdrawal of consent were not given in the remaining 10 cases. Four patients were mistakenly withdrawn by the study team because they had stopped taking their antiepileptic drug medication[8]. One patient was excluded from the analysis because they had surgery to remove a brain tumour between their 3 month and 12 month assessment. Unfortunately, reasons for lack of follow-up were not recorded in every case (n=30). The numbers of patients who withdrew before their three month assessment is

[8] These were mistakenly withdrawn due to early confusion over whether those who stopped taking AEDs should remain in the SANAD Neuropsychology. However, a later decision was made to include these patients (as a potential no treatment control group) and any future cases were considered eligible for 12 month assessment.

also presented in Table 7.1 but as discussed in section 5.3.5, this neuropsychological data will not be presented in this thesis.

Table 7.1: Reasons for withdrawal in those who did not complete the 3 or 12 month assessment

	People with epilepsy		Healthy volunteers
	3 months	12 months	
Study withdrawals, n (%)[ŦŦ]	43 (19)	75 (34)	18 (21)
Reasons for withdrawal, n (%)			
Not eligible	0 (0)	1 (1)	2 (11)
Withdrawn in error	2 (5)	4 (5)	0 (0)
Death	3 (7)	4 (5)	0 (0)
Withdrew consent	11 (26)	14 (19)	6 (33)
Lost to follow-up	12 (28)	22 (29)	10 (56)
Reason not recorded	15 (35)	30 (40)	0 (0)
Completed assessment, n (%)	179 (81)	147 (66)	69 (79)

[Ŧ]percentages for the study withdrawals and completed assessment are expressed as % of those who took part at baseline (i.e. PWE=222 or healthy controls=87). Percentages for the reasons for study withdrawal are expressed as % of withdrawals.

Healthy volunteers

A total of 69 (79.3%) healthy volunteers were reassessed after a median 12 months (range 11-16 months). This was a significantly longer test-retest interval than the patients with epilepsy (z=4179.00, p=.023). However, all the healthy volunteers were assessed within the same period as the patients with epilepsy (i.e. between 9-18 months) so this is not thought to be a meaningful difference. Two healthy volunteers did not complete the 12 month neuropsychological assessment because they had suffered a CNS injury between the baseline and 12 month assessment. One was involved in a serious road traffic accident and one experienced a sporting injury, where they were rendered unconscious for several minutes and they reported still experiencing headaches and poor concentration six months after this incident. Ten healthy volunteers were lost to follow-up (including four who cancelled or did not attend several appointments made for them) and six withdrew their consent to undertake the 12 month assessment. Five cited lack of time as their main reason for not wanting to participate (e.g. due to work commitments, caring for a sick relative) and the other person did not give a reason.

7.3 Demographics and clinical characteristics

Table 7.2 illustrates the demographic characteristics of the 147 patients with epilepsy and the 69 healthy volunteers who completed the 12 month assessment compared with those who did not complete the assessment in each group. There were no differences in sex between the patients with epilepsy and healthy volunteers ($\chi^2(1)=0.42$, $p=.516$). However, the patients with epilepsy were older ($z=4231.00$, $p=.05$). They had a median age of 40 years (range 16-79yrs) at the time of the 12 month assessment compared with a median age of 29 yrs (range 16-81yrs) for the healthy volunteers. As at baseline, there were significant differences in education between the two groups ($\chi^2(2)=27.13$, $p=<.001$). The majority of the patients with epilepsy (56.5%) had 11 years or less of education compared with 21.7% of the healthy volunteers. A lower proportion of patients with epilepsy (15.6%) had more than 15 years of education compared with 42.0% of the healthy volunteers.

There were no differences in sex ($\chi^2(1)=0.50$, $p=.480$) or education ($\chi^2(2)=2.27$, $p=.322$) between patients with epilepsy who did or did not complete the 12 month assessment. Similarly, there were no differences in education ($\chi^2(2)=0.59$, $p=.792$) between healthy volunteers who did or did not complete the 12 month assessment. However, a higher proportion of healthy males dropped out of the study ($\chi^2(1)=6.17$, $p=.013$).

There were no differences in baseline neuropsychological test performance between the healthy volunteers who did or did not complete the 12 month assessment. However, those patients who completed the 12 month assessment had poorer baseline finger tapping scores with the non-dominant hand compared to those who did not participate at 12 months ($t(206)=2.73$, $p=.007$). There were also similar trends for poorer baseline performance in the completers on the finger tapping task with the dominant hand ($t(207)=2.21$, $p=.028$) and the visual reaction time task with the non-dominant hand ($t(204)=-2.44$, $p=.016$). There were no differences on the remaining measures.

Table 7.2: Demographic characteristics of those patients and healthy volunteers who completed the 12 month assessment

Characteristics	PWE assessed (n=147)	Controls assessed (n=69)	PWE not assessed (n=75)	Controls not assessed (n=16)
Sex (n, %)				
Male	73 (49.7)	31 (44.9)	41 (54.7)	14 (77.8)*
Female	74 (50.3)	38 (55.1)	34 (45.3)	4 (22.2)
Median age at 12 mths, yrs (25th-75th centiles)	40 (28-54)	29 (24-50)*	-	-
Education at baseline, yrs (n, %)				
≤11	83 (56.5)	15 (21.7)	50 (66.7)	4 (22.2)
12-15	41 (27.9)	25 (36.2)	15 (20.0)	8 (44.4)
>15	23 (15.6)	29 (42.0)***	10 (13.3)	6 (33.3)
Test-retest interval, mths (25th-75th centiles)	12 (12-12)	12 (12-13)*	-	-

*p<.05, **p<.01, ***p<.001

Table 7.3 illustrates the clinical characteristics of those patients with epilepsy who did and did not complete the 12 month assessment. Of those who completed the assessment, eight (5.4%) had a neurological deficit and 27 (18.4%) had a previous or current neurological disorder at the time of the baseline assessment. Twenty-eight (19.0%) had either a prior neurological deficit or disorder. There were no significant differences in the number of patients with either a prior neurological deficit or disorder between those who did or did not complete the 12 month assessment ($\chi^2(1)=1.14$, $p=.285$).

Patients with prior neurological disorders or known cerebral pathology were excluded from the analysis in the previous chapter, as the aim was to understand the cognitive impact of epilepsy at the time of diagnosis without the impact of other pre-existing neurological conditions or structural lesions. However, this analysis is investigating cognitive change in patients with newly diagnosed epilepsy over time. As these are conditions that are not thought

to present with progressive neurological disease and those with progressive neurological disease were excluded from SANAD, these patients will not be excluded from this analysis.

Of those who completed the 12 month assessment, 137 (93.2%) had an EEG undertaken at baseline and 135 (91.8%) had a CT or MRI scan. Of these, 63 (46.0%) had an abnormal EEG, 67 (48.9%) had a normal EEG and EEG reports were unavailable for seven (5.1%) patients. Scans were abnormal for 35 (25.9%) patients; normal for 90 (66.7%) and reports were unavailable for 10 (7.4%) patients. For those who did not complete the 12 month assessment, 67 (89.3%) had an EEG undertaken at baseline and 69 (92%) had a CT or MRI scan. Of these, 26 (38.8%) had an abnormal EEG, 35 (52.2%) had no abnormality and 6 (9.0%) did not have an EEG report. Scans were abnormal for 14 (20.3%) patients, were normal for 46 (66.7%) and reports were unavailable for nine (13.0%) patients.

Table 7.3: Clinical characteristics at baseline of those who did or did not complete the 12 month assessment

Characteristics	PWE assessed (n=147)	PWE not assessed (n=75)
History at baseline (n, %)		
Neurological deficit	8 (5.4)	1 (1.3)
Neurological disorder (n, %)		
Stroke/cerebrovascular	8 (5.4)	2 (2.7)
Intracranial surgery	2 (1.4)	1 (1.3)
Head injury	2 (1.4)	4 (5.3)
Meningitis/encephalitis	3 (2.0)	0 (0.0)
Other	13 (8.9)	4 (5.3)
EEG (n, %)		
Abnormal EEG	63 (46.0)	26 (38.8)
Non-specific abnormality	22 (34.9)	12 (46.2)
Generalised abnormality		
o Slow wave activity with spiking	9 (14.3)	4 (15.4)
o Slow wave activity without spiking	5 (7.9)	3 (11.5)
Focal abnormality		
o Paroxysmal slow activity with spiking	17 (27.0)	5 (19.2)
o Paroxysmal slow activity without spiking	10 (15.9)	2 (7.7)
CT/MRI (n, %)		
Abnormal scan	35 (25.9)	14 (20.3)

As shown in Table 7.4, there were no differences in seizure type between those who did or not complete the 12 month assessment ($\chi^2(2)=0.07$, $p=.966$). Of those who completed the assessment, the majority experienced partial seizures (72.1%). The majority (71.4%) were classified as having symptomatic or cryptogenic partial epilepsy; 12.2% had idiopathic generalised epilepsy; 15% had unclassified epilepsy; one (0.7%) had idiopathic partial epilepsy and one (0.7%) was classified as having an other epilepsy syndrome. They experienced a median number of three seizures since their baseline assessment (IQR 0-18, range 0-1760) and the majority (66.0%) experienced no tonic-clonic seizures since baseline (IQR 0-1, range 0-76). The person who reported experiencing 1760 seizures during the first 12 months had a combination of myoclonic and typical absence seizures. A total of 46 (31.3%) patients were seizure free during the first 12 months and none of the patients reported experiencing episodes of status epilepticus.

Table 7.4: Epilepsy-related characteristics of those who did or did not complete the 12 month assessment

Characteristics	PWE assessed (n=147)	PWE not assessed (n=75)
Seizure type at baseline (n, %)		
Partial	106 (72.1)	54 (72.0)
Generalised	19 (12.9)	9 (12.0)
Unclassified	22 (15.0)	12 (16.0)
Epilepsy syndrome at baseline (n, %)		
Idiopathic partial		
Childhood epilepsy with occipital paroxysms	1 (0.7)	0 (0.0)
Symptomatic or cryptogenic partial		
Temporal lobe	41 (27.9)	16 (21.3)
Frontal lobe	5 (3.4)	3 (4.0)
Parietal lobe	3 (2.0)	2 (2.7)
Occipital lobe	1 (0.7)	3 (4.0)
Partial epilepsy localisation not specified	55 (37.4)	30 (40.0)
Idiopathic generalised (IGE)		
Juvenile absence	1 (0.7)	1 (1.3)
Juvenile myoclonic	9 (6.1)	1 (1.3)
Tonic-clonic seizures on awakening	1 (0.7)	1 (1.3)
Other IGE not specified	7 (4.8)	4 (5.3)
Other syndrome	1 (0.7)	1 (1.3)
Unclassified	22 (15.0)	13 (17.3)

Information was collected from the healthy volunteers at the 12 month assessment on their experience of life events or medical problems since baseline. Five reported experiencing events but these were not considered have a significant impact on cognition to warrant exclusion from the study. One had experienced episodes of vertigo; one had been taking medication for low thyroid; one had sought medical treatment for gastric problems; one had a baby and one had recently become a father.

Antiepileptic drug treatment

After their baseline assessment, patients with epilepsy started to take their randomised antiepileptic drug. Figure 7.1 illustrates the numbers of patients randomised to each antiepileptic drug group. This figure combines those who were randomised to both Arm A and Arm B, which is why higher numbers of patients have been randomised to lamotrigine and topiramate compared with the other drug groups. These drugs were involved in both arms of the study. The lower numbers of patients randomised to valproate, may reflect the reluctance of clinicians to randomise women of child-bearing age into Arm B, due to the teratogenic effects associated with valproate (e.g. Adab *et al.,* 2004).

After 12 months, 104 (70.7%) patients had remained on their randomised drug for the duration of the 12 month period; six (4.1%) were on their randomised drug but in a polytherapy combination; two (1.4%) were on their randomised drug but had tried others in between and 35 (23.6%) had changed drugs. Of those who had not remained on their randomised AED, 25 (58.1%) had altered their medication due to unacceptable side effects; 15 (34.9%) due to inadequate seizure control; one (2.3%) due to inadequate seizure control and unacceptable adverse events; one (2.3%) patient admitted to being non-compliant with their medication (carbamazepine) and one (2.3%) stopped taking their medication (topiramate) because of life events. During the first 12 months, 19 patients (12.9%) reported experiencing adverse events that were classified as cognitive (e.g. memory problems, confusion and difficulty thinking).

As discussed in section 5.3.3, a power calculation showed that 50 patients were needed in each drug group to detect medium-sized differences between the different AEDs. However, as Figure 7.1 shows, the numbers randomised to each drug group fell short of this. Only

lamotrigine and topiramate exceeded the 50 required. Furthermore, the numbers of patients who remained on their randomised medication for the duration of the 12 month period were small. This varied between nine patients for valproate to 27 for topiramate. Therefore, this study is underpowered to detect anything other than the largest differences between drugs. However, this thesis aims to compare the differences between the cognitive performance of people with epilepsy and healthy volunteers over the first 12 months rather the differential cognitive side effects of AEDs.

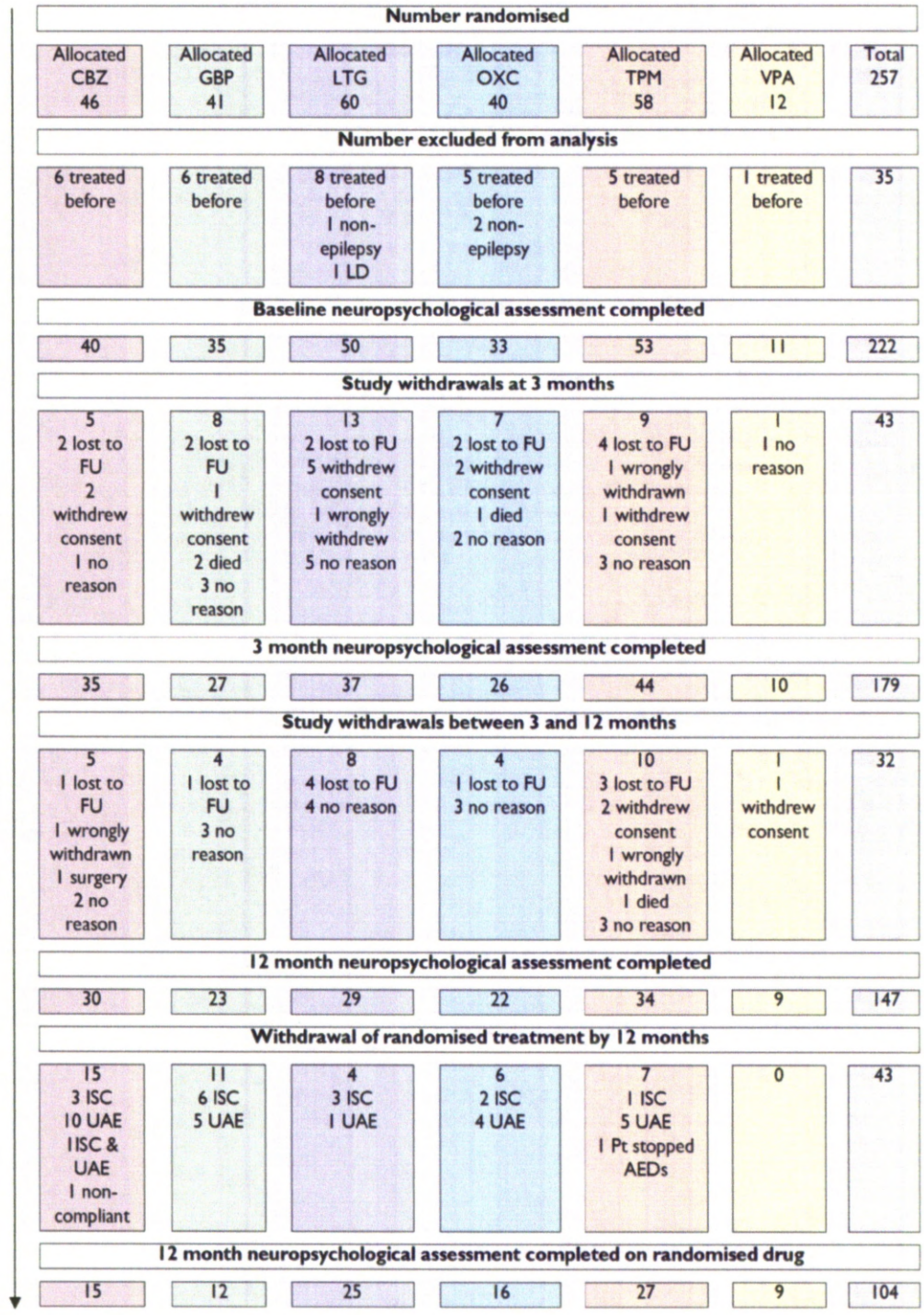
To further illustrate the difficulties in evaluating the cognitive side effects of AEDs in this particular study, Table 7.5 shows the number of patients taking each antiepileptic drug at the time of the 12 month assessment. The majority of patients (95.2%) were treated with monotherapy. The most commonly prescribed drug at the 12 month assessment was topiramate (23.8%) closely followed by lamotrigine (23.1%). Levetiracetam is a relatively new AED and this was prescribed to three patients (2.0%) as monotherapy at the time of the 12 month assessment. Six patients (4.1%) were treated in polytherapy with six different antiepileptic drug combinations.

Table 7.5: AED medication taken at the time of the 12 month assessment

Monotherapy	**N (%)**	**Polytherapy**	**N (%)**
TPM	35 (23.8)	CBZ + CLB	1 (0.7)
LTG	34 (23.1)	CBZ +LEV	1 (0.7)
CBZ	24 (16.3)	GBP + CBZ	1 (0.7)
OXC	16 (10.9)	GBP + OXC	1 (0.7)
VPA	15 (10.2)	LTG + LEV	1 (0.7)
GBP	13 (8.8)	OXC + LTG	1 (0.7)
LEV	3 (2.0)		
Total	**140 (95.1)**	**Total**	**6 (4.1)**
Non-compliant	1 (0.7)		

CLB=clobazam

Figure 7.1: Flow diagram of the patients involved in the SANAD Neuropsychology study



LD=learning disability; FU=follow-up; ISC=inadequate seizure control; UAE= unacceptable adverse event

7.4 The shorter term changes

7.4.1 Changes in neuropsychological functioning

Table 7.6 illustrates the performance of the patients with epilepsy and healthy volunteer groups at baseline and 12 months. During the first 12 months, patients with epilepsy experienced significant declines in performance on five measures. This contrasts with the performance of the healthy volunteer group who only experienced a significant decline on one measure and experienced significant improvements in performance on four measures.

Patients with epilepsy had poorer performance after 12 months on the visual reaction time task with the non-dominant hand (z=-4.04, p<.001). They crossed through fewer digits on the psychomotor speed task of the AMIPB (t(139)=2.77, p=.006); they remembered fewer words both immediately (t(146)=3.19, p=.002) and after a delay (t(146)=3.50, p=.001) on the Rey Auditory Verbal Learning Task and generated fewer words on the verbal fluency task (t(145)=4.08, p=<.001). There was also a trend for them to recognise fewer words on the simultaneous recognition of words task (t(135)=2.40, p=.018) after 12 months.

The healthy volunteers remembered fewer words on the delayed sub-test of the Rey Auditory Verbal Learning Task (t(68)=2.49, p=.015) but were able to remember more story units after a delay on the story recall task (t(68)=-2.88, p=.005). They also had a trend towards recognising more figures on the serial recognition of figures task (t(66)=-2.09, p=.04). They also responded more quickly on the Binary Choice reaction time task (t(66)=2.80, p=.007) and improved on the both the information processing (t(68)=-2.95, p=.004) and psychomotor speed (t(68)=-3.53, p=.001) tasks of the AMIPB.

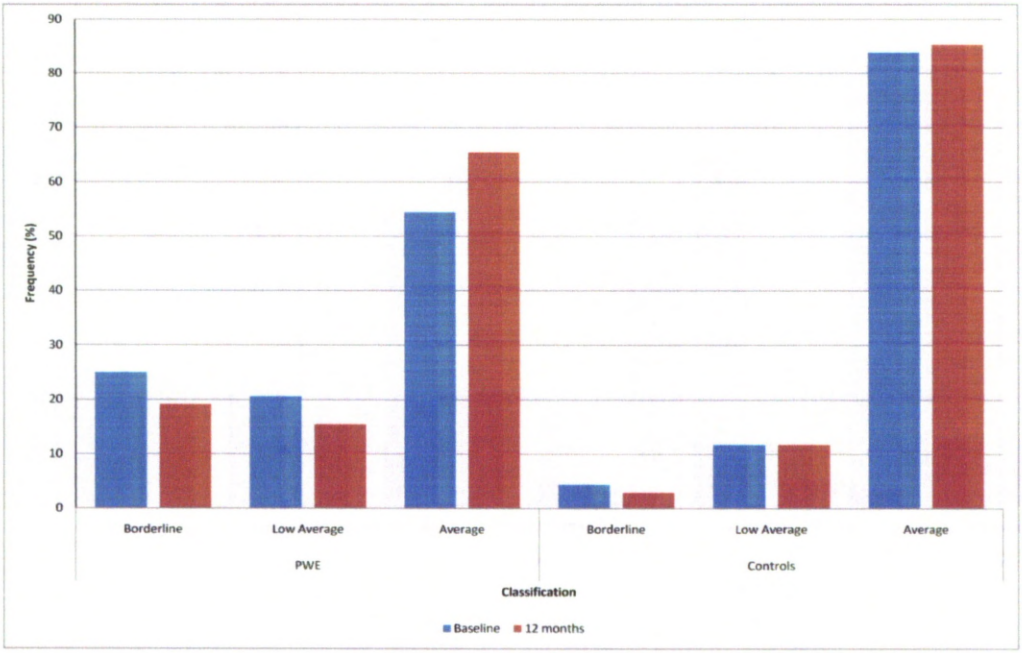
At 12 months, a significantly higher proportion of healthy volunteers were classified as falling in the average range on the Stroop colour word task compared with the patients with epilepsy (85.3% vs. 65.0%). A higher proportion of patients with epilepsy fell in the borderline ranges (19.7% vs. 2.9%) (χ^2(2)=12.06, p=.002). The numbers of people who fell in the average ranges at 12 months increased compared with baseline in both groups, suggesting that both patients with epilepsy and healthy volunteers improved on this task (see Figure 7.2).

Table 7.6: Neuropsychological test performance of patients with epilepsy and healthy volunteers at baseline and 12 months

	PWE		Controls	
Variable	Baseline	12 months	Baseline	12 months
Finger Tapping				
Dominant	55.87 (9.55, 131)	55.17 (9.25, 131)	61.41 (6.51, 61)	62.24 (7.05, 61)
Non-dominant	50.61 (8.60, 131)	49.55 (8.56, 131)	55.40 (5.83, 61)	56.10 (6.34, 61)
Visual RT (ms) †				
Dominant	316.86 (76.33, 128)	332.04 (100.73, 128)	311.93 (45.05, 68)	314.43 (44.45, 68)
Non-dominant	293.00 (266.75-347.25, 130)	311.50 (279.00-392.25, 130)***	314.84 (49.47, 68)	316.69 (36.95, 68)
BCRT (ms) †	383.70 (107.31, 132)	376.20 (110.65, 132)	368.40 (58.23, 67)	351.07** (63.47, 67)
CVST (s) †	10.88 (3.17, 131)	11.12 (3.61, 131)	10.00 (3.17, 67)	10.04 (3.31, 67)
Word recognition				
Serial	15.23 (4.06, 137)	15.20 (4.55, 137)	16.22 (4.02, 68)	17.01 (4.33, 68)
Simultaneous	19.18 (3.44, 136)	18.43 (3.76, 136)*	20.24 (2.77, 63)	20.19 (3.29, 63)
Fig recognition				
Serial	13.99 (3.72, 132)	14.61 (4.14, 132)	16.64 (4.25, 67)	17.69 (4.02, 67)*
Story recall				
Immediate	7.84 (2.80, 147)	7.62 (3.38, 147)	10.11 (3.32, 69)	10.57 (3.70, 69)
Delayed	6.84 (3.00, 147)	6.93 (3.32, 147)	9.31 (3.27, 69)	10.25 (3.88, 69)**
Rey AVLT				
Immediate	44.85 (9.11, 147)	42.57 (9.62, 147)**	51.25 (9.34, 69)	49.62 (9.45, 69)
Delayed	8.52 (3.25, 147)	7.73 (3.08, 147)***	10.62 (3.20, 69)	9.96 (2.87, 69)**
Verbal fluency	35.45 (11.54, 146)	32.32 (11.06, 146)***	42.16 (10.66, 69)	41.75 (9.91, 69)
AMIPB				
Info Processing	59.40 (16.48, 147)	59.15 (17.85, 147)	68.54 (16.25, 69)	70.58 (16.48, 69)**
Motor speed	46.28 (10.26, 140)	44.25 (9.70, 140)**	51.99 (7.76, 69)	54.02 (8.69, 69)***

Values reported are means and SD or medians and 25th-75th percentiles and corresponding n, † higher score means worse performance, *p<.05, ** p<.01, *** p<.001

Figure 7.2: Performance of people with epilepsy and healthy volunteers at baseline and 12 months on the Stroop colour-word task



7.4.2 Changes in the ABNAS

Despite experiencing significant declines on objective measures of cognitive functioning, there were no changes in the frequency of self-reported cognitive complaints between the baseline and 12 month assessments. However, as illustrated in Table 7.7, memory and cognitive slowing problems were the most commonly reported problems by people with epilepsy at 12 months, which were the domains that experienced significant declines.

Table 7.7: Changes in self-reported cognitive complaints between baseline and 12 months

	PWE (median, 25th-75th centiles, n)	
Variable	Baseline	12 months
Memory	33.33 (16.67-58.33, 143)	33.33 (16.67-58.33)
Slowing	33.33 (13.33-60.00, 143)	33.33 (13.33-53.33, 143)
Fatigue	33.33 (13.33-46.67, 143)	26.67 (6.67-53.33, 143)
Concentration	25.00 (8.33-50.00, 143)	25.00 (8.33-41.67, 143)
Language	22.22 (11.11-44.44, 143)	22.22 (11.11-44.44, 143)
Motor	11.11(0.00-33.33, 143)	11.11 (0.00-22.22)

Values reported are medians and 25th-75th percentiles and corresponding n, † higher score means a more negative mood state, *p<.05, ** p<.01, *** p<.001

7.4.3 Standardised regression-based *z*-scores

Table 7.8 reports the predicted 12 month score for the patients with epilepsy based on the regression equations derived from the healthy volunteer group. These take into account practice effects, regression to the mean as well as other factors that affect re-test performance (i.e. baseline performance, age, sex and education). Table 7.8 also shows the difference between the observed and predicted 12 month score; the corresponding standardised regression-based *z*-score and the *p*-value for the difference between the observed and predicted 12 month scores.

After 12 months of treatment, patients with epilepsy were performing significantly lower than expected on 12 of the 15 neuropsychological test variables, with a trend towards significance on the immediate story recall task ($t(146)=-2.31$, $p=.023$). They performed as expected on the binary choice reaction time task ($t(131)=0.00$, $p=.998$). Interestingly, patients performed significantly better than expected on the Computerised Visual Search task ($t(130)=-3.22$, $p=.002$).

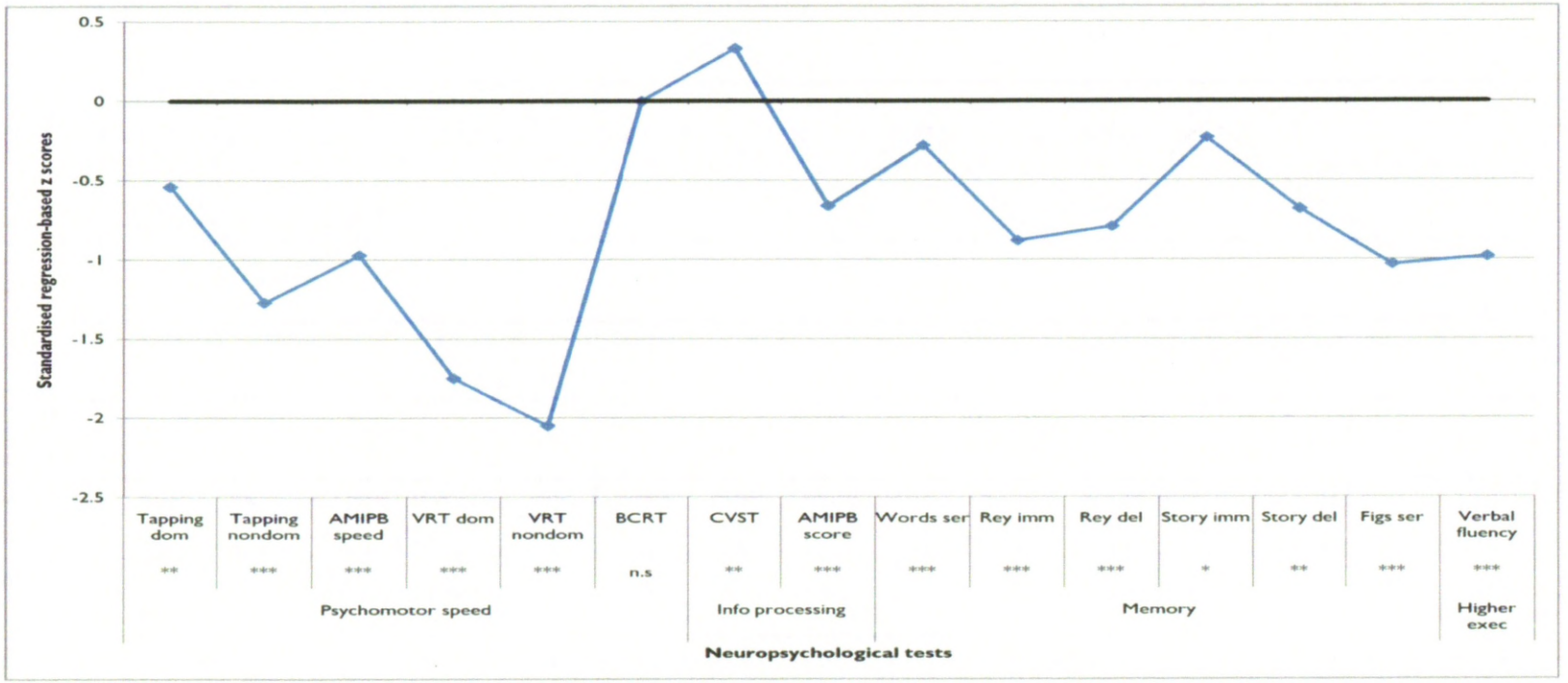
Table 7.8: Standardised regression-based z-scores for the patients with epilepsy

Variable	Predicted 12 month	Observed vs. Predicted	SRB z-score	*p*-value
Finger Tapping				
Dominant	57.66	-2.50	-0.54	.002**
Non-dominant	53.88	-4.34	-1.27	<.001***
Log Visual RT				
Dominant	5.88	-0.20	-1.75	<.001***
Non-dominant	5.63	-0.19	-2.05	<.001***
BCRT	376.18	-0.02	0.00	.998
Log CVST	2.43	0.07	0.33	.002**
Word recognition				
Serial	16.14	-0.94	-0.28	.001***
Figure recognition				
Serial	17.99	-3.39	-1.03	<.001***
Story recall				
Immediate	8.19	-0.57	-0.23	.023*
Delayed	8.66	-1.72	-0.68	<.001***
Rey AVLT				
Immediate	48.18	-5.61	-0.88	<.001***
Delayed	9.20	-1.48	-0.79	<.001***
Verbal fluency	38.15	-5.84	-0.98	<.001***
AMIPB				
Info Processing	62.92	-3.77	-0.66	<.001***
Psychomotor speed	48.87	-4.62	-0.97	<.001***

*p<.05, **p<.01, ***p<.001

Figure 7.3 plots the performance of patients with epilepsy across the neuropsychological test battery with the x-axis representing their expected 12 month performance. Performance on the visual reaction time task, particularly with the non-dominant hand, was the most affected with patients performing more than 2SD below their predicted re-test score. For the majority of the remaining measures, patients were performing between 0.5SD and 1SD below expected.

Figure 7.3: Mean performance of people with epilepsy at 12 months relative to expected performance (represented by the x axis)



*p<.05, **p<.01, ***p<.001, n.s = non-significant

7.5 Impact of epilepsy, seizures and mood related variables

7.5.1 Impact of number of seizures

There were no relationships between the number of seizures since baseline and any of the neuropsychological test measures (see Table 7.9). Although, there was a trend for serial recognition of words to be negatively associated with number of tonic-clonic seizures (r_s= -.197, p=.021).

Table 7.9: Impact of number of seizures on 12 month performance

Variable	No of seizures	No of tonic-clonic seizures
Finger Tapping		
Dominant	.020 (0.817, 131)	-.099 (.260, 131)
Non-dominant	.027 (0.758, 131)	-.142 (.107, 131)
Log Visual RT		
Dominant	.072 (0.420, 128)	-.057 (.524, 128)
Non-dominant	-.022 (.806, 130)	-.109 (.215, 130)
BCRT	.071 (.420, 132)	.017 (.843, 132)
Log CVST	-.041 (.641, 131)	-.065 (.459, 131)
Word recognition		
Serial	-.072 (.403, 137)	-.197 (.021, 137)*
Figure recognition		
Serial	-.031 (.726, 132)	-.027 (.762, 132)
Story recall		
Immediate	-.045 (.588, 147)	-.091 (.271, 147)
Delayed	-.119 (.151, 147)	-.141 (.089, 147)
Rey AVLT		
Immediate	-.082 (.326, 147)	-.101 (.223, 147)
Delayed	-.100 (.228, 147)	-.076 (.363, 147)
Verbal fluency	.095 (.256, 146)	.054 (.518, 146)
AMIPB		
Info Processing	-.038 (.647, 147)	-.025 (.760, 147)
Psychomotor speed	.024 (.774, 140)	.003 (.967, 140)

Values presented are Spearman's correlation coefficients (p-values and n); *p<.05, **p<.01, ***p<.001.

There were no differences in regression-based z-scores between those who had been seizure free for the 12 month period and those who had experienced seizures. However, there was a trend towards who had remained seizure free to perform worse on verbal fluency task (t(144)=2.03, p=.044).

7.5.2 Impact of seizure type

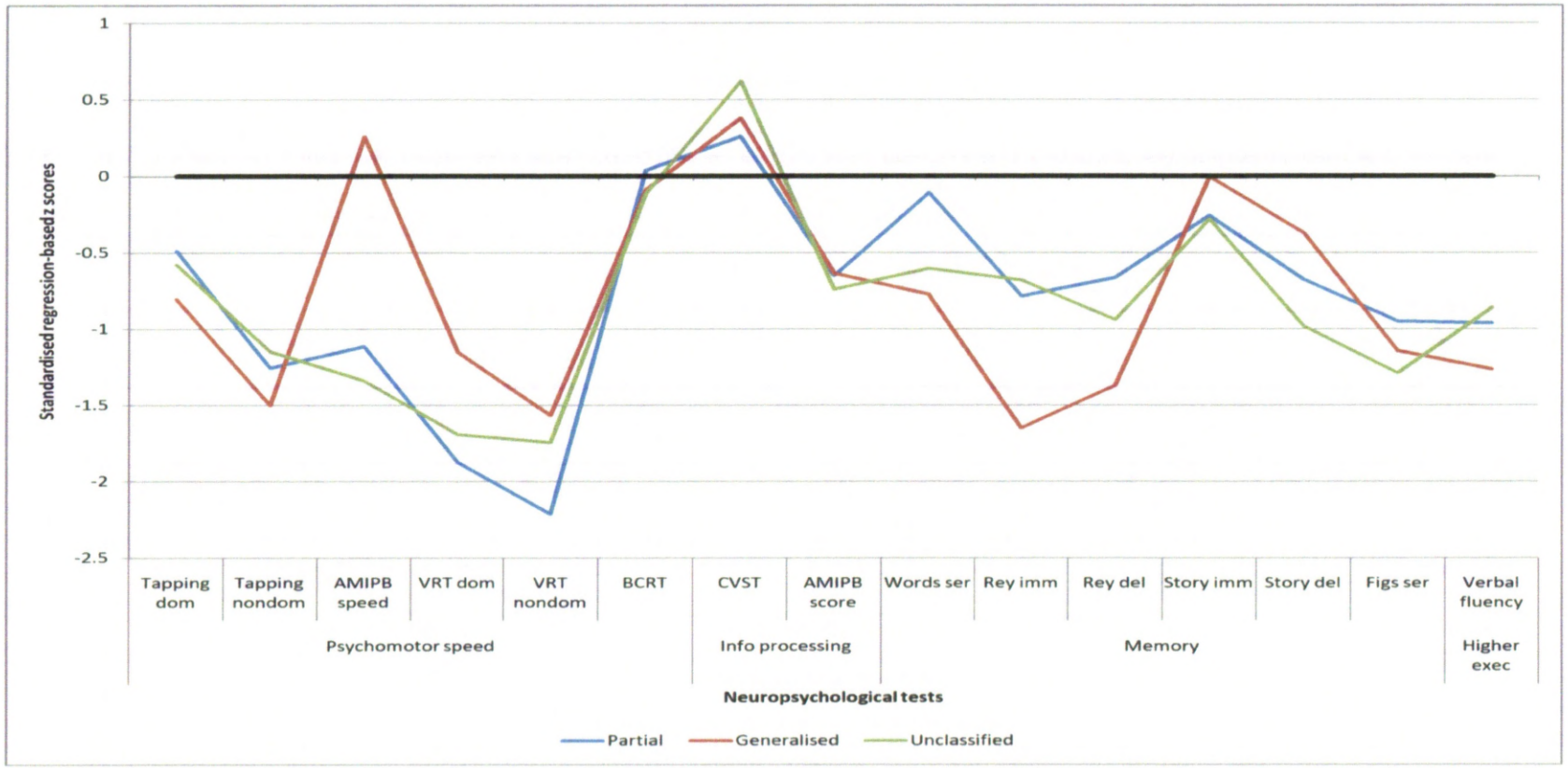
Figure 7.4 plots the performance of patients with partial, generalised and unclassified epilepsy across the neuropsychological test battery, with the x axis representing expected performance. The pattern of change across the neuropsychological test battery is similar across the three groups, however, those with generalised seizures perform better than the other two groups on the psychomotor speed sub-test of the Adult Memory and Information Processing Battery ($F_{2,144}$=5.723, p=.004) but perform worse on the immediate subtest of the Rey Auditory Verbal Learning Test ($F_{2,144}$=4.50, p=.013). Further, those with partial epilepsy perform better than those with generalised epilepsy on the serial recognition of words ($F_{2,134}$=5.44, p=.005). However, these results should be interpreted with caution due to the unequal numbers in each group.

7.5.3 Impact of mood

Changes in mood

As shown in Table 7.10, patients with epilepsy reported experiencing significantly fewer symptoms of tension over the first 12 months of treatment (t(145)=3.74, p<.001). There were no changes in the other mood factors. The healthy volunteers reported significantly fewer symptoms of tension (t(68)=2.78, p=.007) and depression (z=-2.73, p=.006) at their 12 month assessment. There was also a trend for them to report fewer symptoms of anger (t(68)=2.52, p=.014) and confusion (t(68)=2.49, p=.015).

Figure 7.4: Mean performance of those with partial, generalised and unclassified epilepsy at 12 months relative to expected performance(represented by the x-axis)



At 12 months, people with epilepsy had significantly more symptoms of tension ($t(213)=-3.62$, $p<.001$), depression ($t(213)=-4.25$, $p<.001$), anger ($t(213)=-2.32$, $p=.022$), confusion ($t(213)=-4.57$, $p<.001$) and less vigour ($t(213)=3.82$, $p<.001$) than the healthy volunteers.

Table 7.10: Changes in mood in patients with epilepsy and healthy volunteers between baseline and 12 months

	PWE		Controls	
Variable	Baseline	12 months	Baseline	12 months
Tension†	41.88 (21.97, 146)	35.12 (24.59, 146)***	29.91 (21.28, 69)	23.59 (14.20, 69)**
Depression†	22.50 (19.76, 146)	21.16 (21.14, 146)	8.33 (3.33-23.33, 169)	8.33 (1.37-15.83, 169)**
Anger†	21.21 (18.21, 145)	21.39 (20.25, 145)	19.75 (18.01, 69)	14.79 (16.27, 69)*
Vigour	39.49 (19.95, 146)	41.03 (20.69, 146)	50.68 (16.67, 69)	51.86 (16.24, 69)
Fatigue†	40.52 (25.14, 145)	40.17 (27.73, 145)	38.98 (22.39, 69)	34.94 (19.35, 69)
Confusion†	40.39 (21.73, 145)	37.86 (22.30, 145)	29.50 (19.39, 69)	24.43 (13.57, 69)*

Values reported are means and SD or medians and 25th-75th percentiles and corresponding n, † higher score means a more negative mood state, *$p<.05$, ** $p<.01$, *** $p<.001$

Relationships with mood

For the patients with epilepsy, current mood state was significantly associated with the regression-based z-scores for several of the neuropsychological test variables (see Table 7.11). Higher levels of depression were significantly associated with lower regression-based z-scores for the visual reaction time with the dominant hand. Poorer z-scores on the visual reaction time task with the non-dominant hand were significantly associated with higher symptoms of depression and anger. Higher levels of tension, depression and anger were associated with lower regression-based z-scores for psychomotor speed on the AMIPB. Higher levels of vigour were associated with higher regression-based z-scores on the visual reaction time task with the dominant hand.

Table 7.11: Impact of mood on performance at 12 months

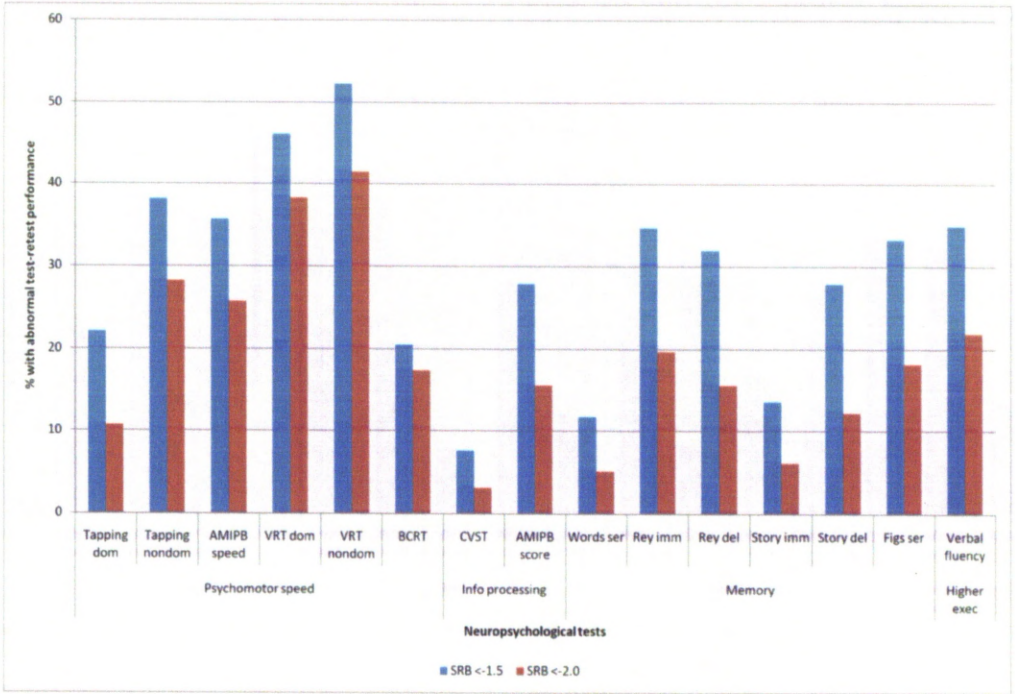
Variable	Tension	Depression	Anger	Vigour	Fatigue	Confusion
Finger Tapping						
Dominant	-.012 (.892, 130)	-.030 (.737, 130)	-.096 (.278, 130)	.087 (.327, 130)	.012 (.893, 130)	.029 (.743, 130)
Non-dominant	.003 (.969, 130)	.012 (.895, 130)	-.051 (.567, 130)	.013 (.884, 130)	-.011 (.897, 130)	.021 (.808, 130)
Log Visual RT						
Dominant	-.192 (.030, 127)*	-.230 (.009, 127)**	-.191 (.032, 127)*	.245 (.006, 127)**	-.197 (.027, 127)*	-.162 (.069, 127)
Non-dominant	-.211 (.016, 129)*	-.253 (.004, 129)**	-.253 (.004, 129)**	.174 (.049, 129)*	-.196 (.026, 129)*	-.194* (.027, 129)
BCRT	.004 (.963, 131)	-.066 (.457, 131)	.007 (.938, 131)	.105 (.231, 131)	.040 (.648, 131)	-.121 (.170, 131)
Log CVST	.045 (.612, 130)	-.061 (.489, 130)	-.035 (.697, 130)	.089 (.314, 130)	-.012 (.892, 130)	-.008 (.930, 130)
Serial word recog	-.024 (.783, 136)	-.036 (.681, 136)	.001 (.995, 136)	.031 (.720, 136)	.008 (.924, 136)	-.127 (.140, 136)
Serial fig recog	-.152 (.082, 131)	-.116 (.188, 131)	-.073 (.409, 131)	.024 (.786, 131)	.054 (.540, 131)	-.144 (.100, 131)
Story recall						
Immediate	-.030 (.717, 146)	-.028 (.738, 146)	.008 (.923, 146)	.056(.506, 146)	.030 (.717, 146)	-.089 (.288, 146)
Delayed	-.089 (.284, 146)	-.120 (.149, 146)	-.056 (.503, 146)	.058 (.487, 146)	-.007 (.930, 146)	-.189* (.022, 146)
Rey AVLT						
Immediate	-.089 (.285, 146)	-.104 (.213, 146)	-.111 (.184, 146)	.078 (.351, 146)	-.066 (.432, 146)	-.170* (.040, 146)
Delayed	-.042 (.616, 146)	-.095 (.252, 146)	.021 (.801, 146)	.191 (.021, 146)*	-.025 (.764, 146)	-.151 (.069, 146)
Verbal fluency	-.074 (.379, 145)	-.025 (.763, 145)	-.015 (.855, 145)	-.004 (.966, 145)	.034 (.686, 145)	-.061 (.466, 145)
AMIPB						
Info Processing	-.038 (.649, 146)	-.100 (.231, 146)	-.090 (.279, 146)	.103 (.216, 146)	.005 (.950, 146)	-.0110 (.186, 146)
Psychomotor speed	-.238 (.005, 139)**	-.257 (.002, 139)**	-.325 (<.001, 139)***	.212 (.012, 139)*	-.179 (.035, 139)*	-.197* (.020, 139)

Values presented are Pearson's correlation coefficients (p-values and n); *p<.05, **p<.01, ***p<.001.

7.6 Individual-level analysis

Figure 7.5 illustrates the proportion of patients with epilepsy who had abnormal scores for each test when different criterions of abnormality were applied (regression-based z-score ≤-1.5 or ≤-2.0). Even when the more conservative criterion was used, a high proportion of patients (41.5%) had abnormal scores on the visual reaction time task with the non-dominant hand and 38.3% had abnormal scores with the dominant hand. Other psychomotor speed measures were also vulnerable to lower than expected re-test performance. On the finger tapping task with the non-dominant hand, 28.2% of patients had abnormal scores and 25.7% had poorer than expected scores on the psychomotor speed task of the Adult Memory and Information Processing Battery. A high proportion of patients (21.9%) also performed lower than expected on the verbal fluency task.

Figure 7.5: The proportion of people with epilepsy with abnormal test scores at 12 months



7.6.1 Impairment index

The regression-based z-scores were used to identify individual patients who had experienced at least one abnormal score across the neuropsychological test battery (see Table 7.12). When the more conservative criterion of a regression-based z-score of ≤-2.0 was applied, 85.0% of patients with epilepsy had some degree of cognitive impairment (> 1 abnormal test score) and 31.3% had abnormal scores on at least a quarter of the test measures. When a regression-based z-score of ≤-1.5 was used as a marker of abnormality, this increased to 94.6% having at least one abnormal test score and 59.9% having abnormal scores on at least a quarter of the tests.

Table 7.12: Number of patients demonstrating abnormal performance across the test battery

Proportion of tests with abnormal scores	Criterion for abnormal performance	
	z-score ≤1.5 (n, %)	z-score ≤2.0 (n, %)
None	8 (5.4)	22 (15.0)
≥1%	139 (94.6)	125 (85.0)
≥25%	88 (59.9)	46 (31.3)
≥50%	17 (11.6)	5 (3.4)

An exploratory data analysis was conducted to investigate the clinical and demographic characteristics of those who were classified as having an abnormal test performance. Table 7.13 illustrates the results of this analysis. There were no significant differences between those who demonstrated an abnormal test performance and those who performed as expected on any demographic, seizure-related and mood-related variables. However, there was a trend for those with lower levels of education ($\chi^2(2)=8.95$, $p<.011$); a higher number of tonic-clonic seizures ($z=-2.04$, $p<.041$) and experiencing higher levels of confusion ($z=-1.96$, $p<.050$) to be in the abnormally performing group.

Table 7.13: Characteristics of those who demonstrated abnormal test performance

Characteristics	Abnormal performance (n=125)	Expected performance (n=22)	Diff (95%CI)	*p*-value
Sex				
Male	63 (50.4)	10 (45.5)	4.9 (-17.0, 25.8)	.669
Female	62 (49.6)	12 (54.5)	-4.9 (-25.8, 17.0)	
Age at 12 mths, yrs	40 (27.50-53.50)	44 (30.50-58.25)	-4 (-11, 4)	.276
Age at first seizure	34 (20-46.50)	26 (17-48.25)	3 (-5, 12)	.403
Education at baseline, yrs				
≤11	75 (60.0)	8 (36.4)	23.6 (1.1, 42.7)	.011*
12-15	35 (28.0)	6 (27.3)	0.7 (-21.6, 17.6)	
>15	15 (12.0)	8 (36.4)	-24.4 (-45.8, -6.4)	
Seizure type at baseline				
Partial	92 (73.6)	14 (63.6)	10.0 (-8.9, 32.1)	-
Generalised	15 (12.0)	4 (18.2)	-6.2 (-27.2, 6.9)	
Unclassified	18 (14.4)	4 (18.2)	-3.8 (-24.9, 9.6)	
Number of seizures	4 (0-19)	2 (0-7)	1 (0, 5)	.201
Number of GTCS	0 (0-1.5)	0 (0-0)	0 (0, 0)	.041*
Immediate 12mth remission	36 (28.8)	10 (45.5)	-16.7 (-38.2, 3.9)	.120
Baseline aetiology/pathology	44 (35.2)	4 (18.2)	17.0 (-4.8, 31.6)	.116
Remained randomised drug	88 (70.4)	16 (72.7)	-2.3 (-19.2, 20.0)	.825
TPM at 12 months	32 (25.6)	3 (13.6)	12.0 (-8.9, 24.8)	.224
Reported cognitive AEs	5 (4.0)	1 (4.5)	-0.5 (-18.1, 5.9)	.905
Mood				
Tension	33.33 (11.11-54.86)	23.61 (13.19-50.69)	5.6 (-5.6, 16.7)	.341
Depression	15.83 (3.75-33.33)	9.17 (3.33-27.08)	5 (-1.67, 11.67)	.214
Anger	14.58 (4.17-33.33)	13.54 (7.29-24.48)	2.1 (-4.2, 10.4)	.673
Vigour	40.63 (25.00-53.13)	46.88 (37.50-65.63)	-9.4 (-18.8, 0)	.060
Fatigue	35.71 (17.86-64.29)	23.21 (13.39-50.00)	7.2 (-3.6, 21.4)	.171
Confusion	35.71 (18.75-60.71	23.21 (14.29-40.18)	10.7 (0, 21.4)	.050*
Classified as impaired at baseline	74 (59.2)	11 (50.0)	9.2 (-12.2, 30.5)	.420

Values reported are either n and % or median with 25th-75th centiles, AEs=adverse events, *p<.05, **p<.01, ***p<.001;

7.7 Summary

The aim of this chapter was to compare the cognitive trajectories of people with epilepsy with healthy volunteers during the first 12 months of epilepsy and its treatment. A total of 147 newly diagnosed previously untreated patients with epilepsy were assessed at baseline and after 12 months. The majority (72.1%) had partial seizures and had experienced a median of three seizures between the baseline and 12 month assessment. None had experienced episodes of status epilepticus. The majority (70.7%) had remained on their randomised drug throughout the 12 month period and 31.3% had achieved an immediate 12 month seizure remission.

There were no differences in demographic or clinical characteristics between those patients who did or did not complete the 12 month assessment. For the majority of measures, there were no differences in baseline neuropsychological performance between those who did or did not complete the 12 month assessment. However, those who completed had poorer baseline finger tapping scores and trends towards poorer scores on the visual reaction time task with the non-dominant hand.

The cognitive profile of patients was compared with 69 healthy volunteers who were recruited from the general population and were also assessed at baseline and after 12 months. They were equated for age and sex at baseline, however after 12 months the healthy volunteers were younger and had significantly more years of education than people with epilepsy. There were no differences in the demographic or baseline neuropsychological characteristics of the healthy volunteers who did or did not complete, although more healthy males dropped out of the study.

After 12 months of treatment, patients with epilepsy experienced significant declines on five measures, in contrast to the healthy volunteers who had a decline on one measure but experienced significant improvements on four measures. The tasks most affected were those that assessed memory, psychomotor speed and higher executive functioning, as assessed by the verbal fluency task.

After taking into account baseline performance, age, sex and education, patients performed significantly worse than expected on 12 out of the 15 neuropsychological test measures. The domains that were most at risk of poor performance were memory, higher executive functioning and psychomotor speed, particularly the visual reaction time task. Interestingly, patients performed significantly better on the Computerised Visual Search Task.

There were no significant relationships between the number of seizures or the number of tonic-clonic seizures since baseline and any of the regression-based *z*-scores. Similarly, there were no differences between those who achieved an immediate 12 month remission and those that did not. There were few differences between patients with partial, generalised and unclassified epilepsy. Patients with generalised epilepsy performed better than the other two groups on the psychomotor speed test of the AMIPB but worse on the immediate subtest of the Rey AVLT and the serial recognition of words compared with those with partial epilepsy. However, these results should be interpreted with caution due to the unequal numbers in each group.

The healthy volunteers reported significantly fewer symptoms of tension and depression at their 12 month assessment. The patients with epilepsy reported fewer symptoms of tension. However, at the time of assessment, people with epilepsy had significantly higher levels of tension, depression, anger and confusion and significantly less vigour than the healthy volunteers. Their current mood state was significantly related to several of the regression-based *z*-scores, suggesting that mood may be related to change in cognitive functioning on measures, particularly those that assess psychomotor speed.

A high proportion of patients were classified as having abnormal scores, particularly on the psychomotor speed measures. A total of 85% of patients had at least one abnormal test score across the neuropsychological test battery. There were no significant differences between those who were classified as having or not having an abnormal test performance on demographic, epilepsy and mood-related variables. However, there were trends for those with had fewer years of education, had experienced higher numbers of tonic-clonic seizures and more symptoms of confusion to be in the abnormally performing group.

A proportion of these patients were followed-up after an average of five years, the results of this analysis will be presented in the next chapter.

Chapter 8 Results: The longer term impact

8.1 Overview of the chapter

This chapter outlines the results of the Neuropsychology follow-up study, which aims to assess cognitive change over a longer term period in a sub-set of patients with epilepsy, who had taken part in the SANAD Neuropsychology study. The numbers of patients who were recruited and assessed as part of this follow-up study will be described. The demographic and clinical characteristics of these patients with epilepsy will be reported. Changes in neuropsychological performance from baseline to follow-up will be analysed and the factors that influence cognitive change will be investigated. The amount of cognitive change experienced at an individual-level will be explored. These results have formed the basis of a peer-reviewed publication by Taylor & Baker (in press) (see Appendix D).

8.2 Participants

8.2.1 Recruitment

A total of 144 patients had completed all three assessments from the participating hospital centres. As shown in Table 8.1, seven patients had died since their 12 month assessment and one patient had undergone epilepsy surgery. A further two patients had requested, as part of the SANAD trial and associated quality of life study, that no further requests to take part in research be made. Therefore, 134 patients were eligible for the study. Despite using the NHS tracking system and contacting local hospital centres, up to date contact details could not be found for two patients (one from Royal Hallamshire Hospital and one from Glan Clwyd Hospital). Invitation letters and participant information sheets were sent to 132 patients.

Table 8.1: Number of patients from each centre recruited and assessed in the follow-up study

	WCNN	RBH	UHW	RHH	WMH	GCH	HH	DRI	Total
12 month ass	39	32	30	12	11	8	8	4	144
Not eligible									
Deceased	4	1	0	0	0	0	0	2	7
Surgery	1	0	0	0	0	0	0	0	1
Other	2	0	0	0	0	0	0	0	2
Eligible	32	31	30	12	11	8	8	2	134
Approached	32	31	30	11	11	7	8	2	132
Responded									
Yes	12	8	17	8	4	3	2	0	54
No	12	11	5	1	2	2	4	0	37
No response	8	12	8	2	5	2	2	2	41
Completed	11	7	15	8	4	3	2	0	50

WCNN=Walton Centre for Neurology and Neurosurgery, RBH=Royal Bolton Hospital, UHW=University Hospital of Wales, RHH= Royal Hallamshire Hospital, WMH= Wrexham Maelor Hospital, GCH=Glan Clwyd Hospital, HH= Hope Hospital, DRI=Doncaster Royal Infirmary

8.2.2 Assessment

Ninety-one patients (69%) either returned the reply slip or responded to telephone calls. There was no response from 41 (31%) patients, despite telephone calls and follow-up letters being made. Of those approached, 54 (41%) patients wanted to take part but 37 (28%) refused. Reasons for not wanting to take part included: ill health (n=3); did not feel they had the time (n=2); family or work circumstances [work commitments (n=2), pregnancy (n=1), family bereavement (n=1)]; tired of taking part in research (n=1); no longer had epilepsy so did not want to contribute (n=1) or a reason was not given (n=26).

Of the 54 patients who wanted to take part, 50 completed the follow-up assessment. Assessments were not completed for four patients for various reasons: the frequency and severity of seizures made it too difficult to carry out an assessment for one patient; one cancelled their appointment and did not want to rearrange, and after responding to the invitation letter, contact could not be made with two patients to arrange an assessment time.

8.3 Demographic and clinical characteristics

Table 8.2 illustrates the clinical and demographic characteristics of the 50 patients who completed the neuropsychology follow-up assessment. The majority (62%) were females with an average age of 46 yrs, ranging from 21-84 years. It was a mean 64 months since their baseline assessment, ranging from 43 months to 85 months. This test-retest interval will be used as surrogate for duration of epilepsy, as these patients were newly diagnosed at the time of the baseline assessment. There were no differences in terms of age at baseline ($t(130)=-1.11$, $p=.267$) or gender ($\chi^2(1)=2.184$, $p=.139$) between those who did and did not take part in this follow-up study.

At baseline, the majority of patients with epilepsy (84%) had no previous neurological disorders. However, two had experienced head injuries prior to the first assessment; one had a stroke; one had meningitis; one had intracranial surgery; one had intracranial surgery and an intracerebral abscess; one had idiopathic intracranial hypertension and the other had eclamptic seizures. A higher proportion of those who did not take part in this follow-up study had a neurological deficit at baseline (8.5% vs. 0%). A higher proportion also had previously had a stroke (6.1% vs. 2.0%) or an other neurological disorder (11% vs. 6%). But a higher proportion of patients in this follow-up study had intracranial surgery (4% vs. 0%) or a head injury (4% vs. 0%). However, the differences between the two groups were too small to make statistical comparisons.

At baseline, 44 (88%) of those who took part in follow-up study had a CT/MRI scan. Of these 10 had an abnormal scan, 33 had a normal scan and the report was unavailable for one. The abnormalities were not detailed for eight but were white matter abnormalities and a cavernoma for two patients.

Table 8.2: Clinical and demographic characteristics of those who did or did not take part in follow-up study

Characteristics	Took part in follow-up (n=50)	Eligible but did not take part in follow-up (n=82)
Sex (n, %)		
Male	19 (38.0)	42 (51.2)
Female	31 (62.0)	40 (48.8)
Mean age at baseline, yrs (SD, range)	41.34 (15.01, 15-78)	38.32 (15.20, 15-69)
Mean age at FU, yrs (SD, range)	46.76 (15.22, 21-84)	-
Mean duration, mths (SD, range)	64.24 (10.75, 43-85)	-
History at baseline (n, %)		
Neurological deficit	0 (0)	7 (8.5)
Neurological disorder (n, %)		
Stroke/cerebrovascular	1 (2.0)	5 (6.1)
Intracranial surgery	2 (4.0)	0 (0)
Head injury	2 (4.0)	0 (0)
Meningitis/encephalitis	1 (2.0)	2 (2.4)
Other	3 (6.0)	9 (11.0)
Abnormal imaging at baseline (n, %)	10 (20)	20 (24.4)
Seizure type at baseline (n, %)		
Partial	42 (84.0)	55 (67.1)
Generalised	4 (8.0)	13 (15.9)
Unclassified	4 (8.0)	14 (17.1)
Seizure frequency at FU (n, %)		
None	29 (58.0)	-
Daily	3 (6.0)	-
Weekly	3 (6.0)	-
Monthly	12(24.0)	-
Yearly	3 (6.0)	-
Seizure free previous 12 months (n, %)	29 (58.0)	-
Other co-morbidities (n, %)	20 (40.0)	-

As in SANAD, the majority (84%) had partial epilepsy. There were no differences in baseline seizure type between those who did and did not take part ($\chi^2(2)=4.574$, $p=.102$). The majority (58%) of patients in this study had also been seizure free for at least the 12 months prior to the assessment. Of those who continued to have seizures, three experienced them daily;

three weekly and three experienced only one seizure in the previous year. The remaining twelve reported having them monthly.

Forty per cent of those who took part in the follow-up assessment reported experiencing other medical conditions unrelated to their epilepsy since their 12 month assessment. These included cancer (e.g. carcinoma tumour, cancerous carcinoma on the hand, breast cancer); lymphodema and cellulitis as a result of breast cancer; diabetes; sleep apnoea; surgical procedures (e.g. hysterectomy, gall bladder operation); gynaecological problems; a neck injury affecting the left arm and two reported head injuries. Three patients reported being currently under investigation (one for fainting spells, one for a low cortisol response) and five reported previous psychological problems. Two reported experiencing episodes of depression; one had been hospitalised for a suicide attempt and one had been referred to psychological services for anger management. One patient reported feeling under stress due her husband being ill and other stressful life events; however, she had not sought treatment. Of those who had reported experiencing psychological problems since the 12 month assessment, none reported still experiencing them at the time of the follow-up assessment.

At baseline, 15 (30%) patients were classified as having temporal lobe epilepsy; 1 (2%) as having frontal lobe epilepsy and 26 (52%) as having partial epilepsy but the localisation was not specified. Two (4%) patients were classified as having juvenile myoclonic epilepsy; 1 (2%) as having an other unspecified idiopathic generalised epilepsy and 1 (2%) as having an other epilepsy syndrome. The remaining 8% had unclassified epilepsy.

Two patients reported not taking AEDs at the time of the follow-up assessment. Of those who were taking AEDs, 83.4% were treated with monotherapy and 16.6% with polytherapy. As shown in Table 8.3, lamotrigine, carbamazepine and topiramate were the most commonly prescribed drugs. However, one patient admitted that they were non-compliant with topiramate and self-medicated when they felt they needed to. The eight patients treated with polytherapy were on six different combinations. Three were taking carbamazepine and levetiracetam; one carbamazepine and topiramate; one lamotrigine and valproate; one lamotrigine and clobazam (CLB); one levetiracetam and clobazam and one was on a combination of topiramate and pregabalin. As patients had changed their drugs throughout

the five year period, differences in cognitive functioning between drugs will not be analysed in this thesis.

Table 8.3: AEDs prescribed at the time of the follow-up assessment

Monotherapy	**N (%)**	**Polytherapy**	**N (%)**
LTG	10 (20.0)	CBZ+LEV	3 (6)
CBZ	9 (18.0)	CBZ+TPM	1 (2)
TPM	9 (18.0) [β]	LTG+VPA	1 (2)
GBP	4 (8.0)	LTG+CLB	1 (2)
LEV	4 (8.0)	LEV+CLB	1 (2)
OXC	2 (4.0)	TPM+PGB	1 (2)
PGB	1 (2.0)		
VPA	1 (2.0)		
Total	**40 (80)**	**Total**	**8 (16.0)**
None	**2 (4.0)**		

[β] one patient admitted to being non-compliant with TPM.

At the time of follow-up, half of the patients were in paid employment; one was still in full-time education; 18% had retired and 30% were unemployed. As shown in Table 8.4, they had a median of 12 years of education and 82% had achieved formal educational qualifications. Forty four percent had achieved school-level qualifications (GSCEs/CSEs or equivalent) and 30% had achieved the equivalent of A-levels or higher. They had significantly more years of formal education at baseline than those who were eligible but did not take part in the follow-up study ($\chi^2(2) = 11.30$, $p=.004$). However, there were no differences between the two groups on any of the baseline neuropsychological measures, although there was a trend for those who did not take part to have lower scores on both aspects of the Adult Memory and Information Processing Battery (AMIPB information processing $t(130)=-2.36$, $p=.020$; AMIPB psychomotor speed $t(125)=-2.13$, $p=.035$). Similarly, there were no differences between the two groups on any of the 12 month neuropsychological measures.

Table 8.4: Socio-demographic characteristics of those who did or did not take part in the follow-up study

Characteristics	Took part in follow-up (n=50)	Eligible but did not take part in follow-up (n=82)
Employment status at FU (n, %)		
In paid full/part-time work	25 (50.0)	-
In full-time education	1 (2.0)	-
Retired	9 (18.0)	-
Unemployed	15 (30.0)	-
Median education at FU, yrs (25th-75th centiles)	12 (11-16)	-
Education at baseline, yrs (n, %)		
≤11	20 (40.0)	53 (64.6)**
12-15	17 (34.0)	23 (28.1)
>15	13 (26.0)	6 (7.3)
Highest qualification obtained at FU (n, %)		
None	9 (18.0)	-
Other	2 (4.0)	-
GCSE/CSE or equivalent	22 (44.0)	-
A-levels or equivalent	4 (8.0)	-
Diploma	4 (8.0)	-
Degree or higher	9 (18.0)	-

*p<.05, **p<.01, ***p<.001

8.4 The longer term changes

8.4.1 Changes in neuropsychological functioning

Table 8.5 illustrates the differences between baseline and follow-up on the neuropsychological test variables. Patients with epilepsy had statistically significantly slower reaction times at follow-up on the visual reaction time task with both the dominant (t(45)=-3.85, p<.001) and non-dominant (t(47)=-5.62, p<.001) hand. They also had significantly lower scores at follow-up compared with baseline on the immediate (t(49)=3.92, p<.001) and delayed (z=-3.90, p=.001) tasks of the of the Rey Auditory Verbal Learning Test.

There were also trends for worse performance at follow-up on serial recognition of words ($t(46)=2.35$ $p=.023$); the information processing task of the AMIPB ($t(49)=2.60$, $p=.012$) and on the CVST ($t(45)=-2.29$, $p=.027$). However, there was a trend towards improved performance on the serial recognition of figures task ($t(44)=-2.09$, $p=.043$).

Table 8.5: Changes in neuropsychological test variables from baseline to follow-up

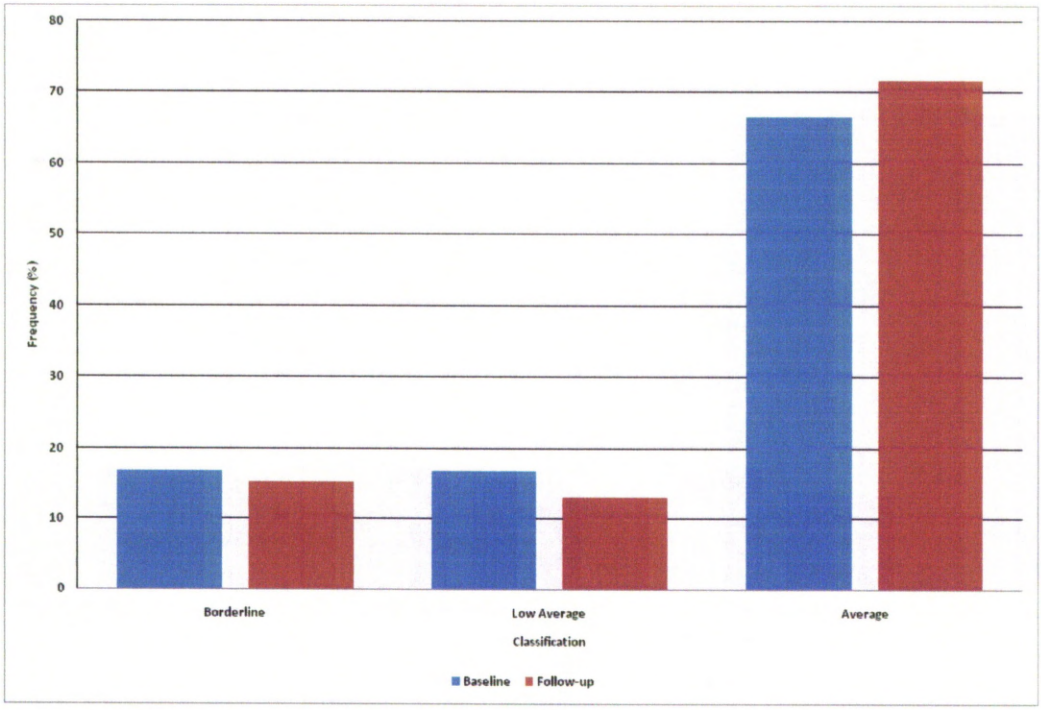
Variable	Baseline	Follow-up	Diff (95% CI)	*p*-value
Finger Tapping				
Dominant	56.02 (9.75, 48)	56.34 (9.23, 48)	-0.32 (-3.42, 2.78)	.836
Non-dominant	51.34 (8.57, 47)	50.43 (6.70, 47)	0.90 (-1.46, 3.26)	.446
Visual RT (ms)†				
Dominant	309.37 (62.97, 46)	348.13 (54.00, 46)	-38.76 (-59.04, -18.48)	<.001***
Non-dominant	311.98 (68.84, 48)	366.33 (68.07, 48)	-54.35 (-73.82, -34.89)	<.001***
Binary Choice RT (ms) †	341.00 (308.00-424.00, 45)	361.00 (313.00-419.00,45)	-7 (-27, -16)	.519
CVST (s)†	10.80 (4.10, 46)	11.87 (3.60, 46)	-1.06 (-2.00, -0.13)	.027*
Word recognition				
Serial	15.94 (4.11, 47)	14.23 (4.75, 47)	1.70 (0.24, 3.16)	.023*
Simultaneous	20.00 (17.00-22.00, 43)	19.00 (17.00-21.00, 43)	0.5 (-0.5, 1.5)	.249
Fig recognition				
Serial	14.29 (4.00, 45)	15.56 (4.65, 45)	-1.27 (-2.49, -0.04)	.043*
Story recall				
Immediate	8.34 (2.64, 50)	7.89 (2.73, 50)	0.45 (-0.24, 1.14)	.197
Delayed	7.20 (2.62, 50)	7.39 (2.88, 50)	-0.19 (-0.90, 0.52)	.593
Rey AVLT				
Immediate	45.88 (9.16, 50)	40.34 (10.79, 50)	5.54 (2.70, 8.38)	<.001***
Delayed	10.00 (7.00-11.00, 50)	8.00 (6.00-10.00, 50)	-1.5(-2, -1)	.001***
Verbal fluency	35.90 (12.48, 50)	35.78 (12.68, 50)	0.12 (-2.69, 2.93)	.932
AMIPB				
Info Processing	63.39 (16.33, 50)	59.80 (18.49, 50)	3.59 (0.81, 6.37)	.012*
Psychomotor speed	48.65 (10.91, 49)	46.71 (9.07, 49)	1.94 (-0.82, 4.70)	.164

Values reported are means and SD or medians and 25th-75th percentiles and corresponding n, † higher score means worse performance, *$p<.05$, ** $p<.01$, *** $p<.001$

Figure 8.1 illustrates the percentage of patients whose performance fell in the different categories at baseline and follow-up on the Stroop colour-word task. A higher proportion of

patients were performing in the average range at follow-up compared with baseline (71.7% vs. 66.7%). Fewer patients were performing in the borderline ranges at follow-up compared with baseline (15.2% vs. 16.7%). This suggests that, as a group, patients improved over time on this task.

Figure 8.1: Changes in classification on the Stroop colour-word task from baseline to follow-up



8.4.2 Changes in mood variables

On the Profile of Mood States questionnaire, as shown in Table 8.6, patients reported feeling significantly fewer symptoms of tension at the follow-up assessment ($t(49)=3.00$, $p=.004$). They also reported fewer symptoms of depression, anger, fatigue and more vigour but reported feeling more confusion. However, none of these changes were statistically significant.

Table 8.6: Changes in mood factors from baseline to follow-up

Variable	Baseline (mean, SD, n)	Follow-up (mean, SD, n)	Diff (95% CI)	*p*-value
Tension†	37.89 (20.19, 50)	29.17 (20.28, 50)	8.72 (2.88, 14.56)	.004**
Depression†	18.80 (16.63, 50)	17.60 (20.02, 50)	1.20 (-3.35, 5.75)	.598
Anger†	19.42 (18.11, 50)	17.50 (20.30, 50)	1.92 (-2.63, 6.47)	.401
Vigour	41.38 (20.33, 50)	44.06 (20.32, 50)	-2.69 (-7.90, 2.53)	.305
Fatigue†	41.14 (25.06, 50)	38.64 (31.13, 50)	2.50 (-5.23, 10.23)	.519
Confusion†	34.07 (20.81, 50)	34.86 (23.32, 50)	-0.79 (-6.08, 4.51)	.767

* $p<.05$, ** $p<.01$, *** $p<.001$

8.4.3 Changes in the ABNAS self-report measure

As shown in Table 8.7, patients reported experiencing less fatigue but more memory, language and concentration problems and cognitive slowing at the follow-up assessment. However, these were not statistically significant changes. Although, not statistically significant, reports of increased cognitive problems in these areas are consistent with the findings of more attention and memory problems at follow-up on the objective measures.

Table 8.7: Changes in the ABNAS self-report measure from baseline to follow-up

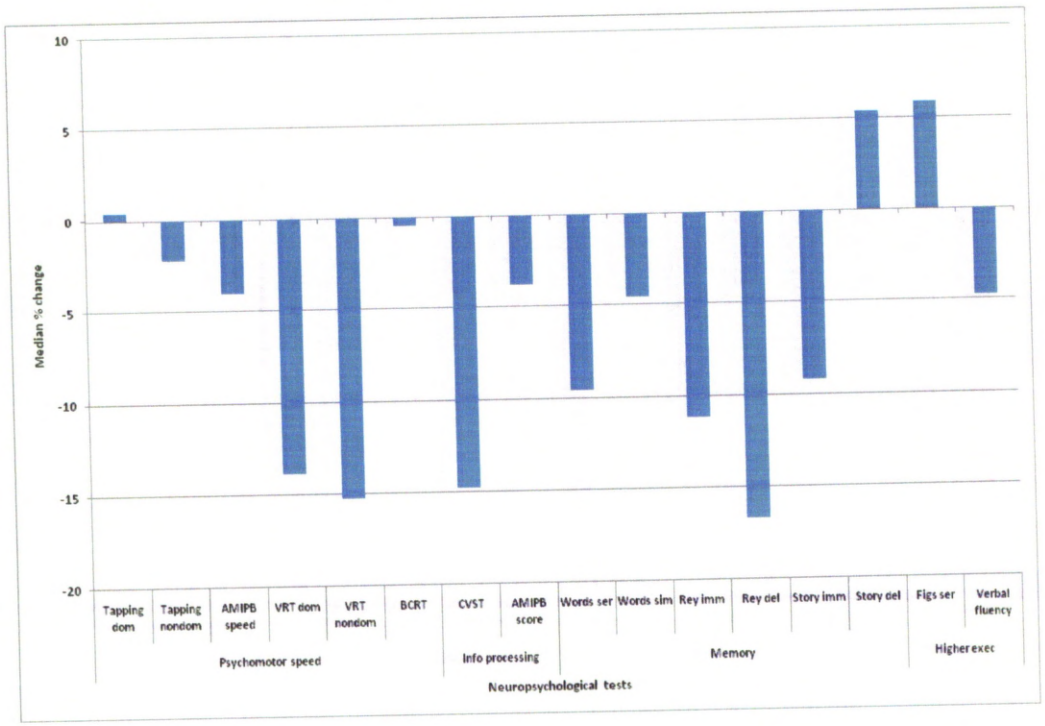
Variable	Baseline (median, 25th-75th centiles, n)	Follow-up (median, 25th-75th centiles, n)	Diff (95% CI)	*p*-value
Fatigue†	30.00 (13.33-51.67, 48)	26.67 (6.67-53.33, 48)	3.33 (-3.33, 6.67)	.658
Slowing†	33.33 (13.33-60.00, 48)	40.00 (13.33-65.00, 48)	-3.33 (-10.00, 3.33)	.509
Memory†	33.33 (16.67-58.33, 48)	41.67 (25.00-66.67, 48)	-4.17 (-12.5, 4.17)	.268
Concentration†	25.00 (8.33-50.00, 48)	33.33 (8.33-50.00, 48)	-4.17 (-12.5, 4.17)	.343
Motor†	11.11 (0.00-22.22, 48)	11.11 (0.00-22.22)	0 (5.56, 0)	.797
Language†	22.22 (11.11-44.44, 48)	27.78 (22.22-55.56)	-5.56 (-11.11, 0)	.063

† higher score means more cognitive complaints, * $p<.05$, ** $p<.01$, *** $p<.001$

8.5 Percentage change

Figure 8.2 plots the median percentage change scores across the neuropsychological test battery. The tests with the most decline from baseline are the delayed sub-test of the Rey Auditory Verbal Learning Task; visual reaction time with the dominant and non-dominant hand and the CVST. This is consistent with the results of the dependent *t* tests. However, the declines are subtle and most measures have on average less than 5% decline from baseline. The Rey Auditory Verbal Learning Task and visual reaction time tasks seem to be the most vulnerable to decline at follow-up, with an average decline of 17% from baseline for the Rey AVLT. Interestingly, improvements were found on the story recall tasks and serial recognition of figures.

Figure 8.2: Median percentage change score across the neuropsychological test battery



8.6 Factors associated with cognitive change

Table 8.8 contains the results of the univariable analyses. There were no differences between those with or without a previous/current neurological disorder or abnormal imaging at baseline; or those who had seizures in the previous year and those who had not for any of the percentage change scores. Similarly, there were no differences between those who had other co-morbid diagnoses, between the 12 month assessment and follow-up and those who did not on any of the scores.

There was a trend for years of education to be significantly associated with change on the delayed story recall task (r_S=.316, p=.025) and duration of epilepsy with simultaneous recognition of words (r_S=-.326, p=.033). Age at the time of the follow-up assessment was significantly associated with psychomotor speed sub-tests of the Adult Memory and Information Processing Battery (r_S=-.442, p=.001) and had trends with the information processing sub-test (r_S=-.321, p=.023) and serial recognition of words (r_S=-.297, p=.042). Scores on the Tension factor of the Profile of Mood States were significantly associated with tapping with the dominant (r_S=-.527, p<.001) and non-dominant hand (r_S=-.383, p=.008); the psychomotor speed sub-test of the Adult Memory and Information Processing Battery (r_S=-.385, p=.006) and a trend with delayed recall (r_S=-.282, p=.047) on the Rey Auditory Verbal Learning Test.

Table 8.8: Univariable analyses of factors affecting cognitive change (values reported are p-values)

Variable	Seizures	Age	Education	Duration	Co-morbidities	Tension	Neurological deficit
Finger Tapping							
Dominant	.530	.770	.999	.280	.509	<.001***	.764
Non-dominant	.983	.813	.834	.778	.965	.008**	.698
Visual RT (ms)							
Dominant	.126	.171	.228	.342	.060	.574	.830
Non-dominant	.442	.077	.882	.580	.359	.055	.456
BCRT (ms)	.963	.323	.421	.417	.694	.161	.634
CVST (s)	.540	.290	.904	.690	.311	.831	.166
Word recog							
Serial	.308	.042*	.489	.708	.435	.381	.832
Simultaneous	.213	.278	.274	.033*	.195	.505	.703
Figure recog							
Serial	.331	.950	.308	.092	.879	.339	.475
Story recall							
Immediate	.302	.836	.120	.341	.559	.119	.617
Delayed	.672	.293	.025*	.521	.112	.887	.573
Rey AVLT							
Immediate	.875	.317	.254	.903	.205	.153	.518
Delayed	.783	.788	.567	.677	.905	.047*	.546
Verbal fluency	.331	.525	.295	.145	.607	.932	.924
AMIPB							
Info Processing	.387	.023*	.580	.693	.759	.425	.130
Motor speed	.808	.001***	.928	.834	.200	.006**	.386

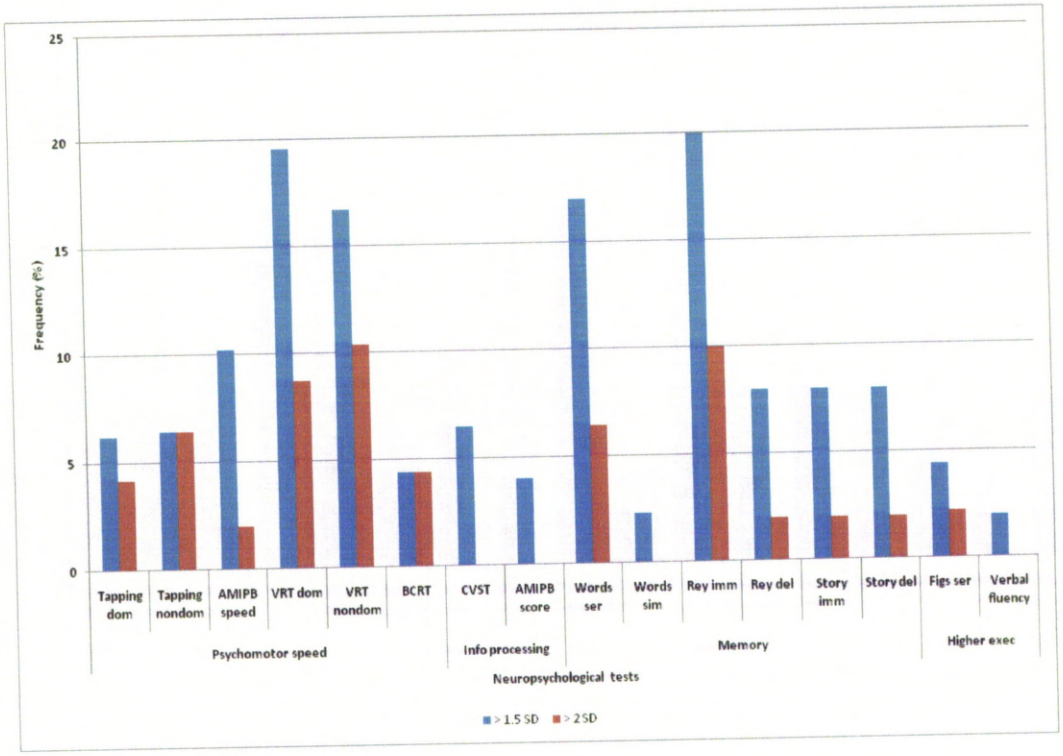
*$p<.05$, **$p<.01$, ***$p<.001$

8.7 Individual change

Figure 8.3 illustrates the percentage of patients who experience cognitive decline across each of the measures when the different criterions (i.e. >1.5 SD or >2SD) of decline were applied. Using a more liberal criterion of 1.5SD, 20.0% of patients experienced cognitive decline on the immediate subtest of the Rey Auditory Verbal Learning Test; 19.6% on the visual reaction time with the dominant hand; 16.7% with the non-dominant hand and 17.0% on the recognition of words serially. However, when a more conservative criterion of 2SD was employed, the number of patients experiencing cognitive decline decreased. Only 10.0% were

still classified as experiencing decline on the delayed recall of the Rey Auditory verbal Learning Test; 10.4% on the non-dominant hand visual reaction time task and 8.7% with the dominant hand. The proportions classified as declined on the serial recognition of words also decreased to 6.4%. Again, it appears that the Rey Auditory Verbal Learning test and visual reaction time tasks are more vulnerable to decline in a sub-set of patients with epilepsy.

Figure 8.3: The proportion of patients who declined by more than 1.5 and 2SD between baseline and follow-up



Those patients who had experienced cognitive decline on at least one neuropsychological test measure were identified. Table 8.9 illustrates that 64% of patients had experienced a decline of more than 1.5 SD from baseline on at least one test measure. This figure reduced to 38% when the more conservative value of 2SD was applied. Only one patient had cognitive declines on more than a quarter of the test measures[9].

[9] After this patient's assessment, under the supervision of Prof GA Baker, a letter was sent to the GP informing them of the significant declines that had been observed and the difficulties that this patient had in completing

Table 8.9: Number of patients demonstrating cognitive decline across the test battery

Proportion of tests declined	Criterion for cognitive decline	
	1.5 SD (n, %)	2SD (n, %)
None	18 (36.0)	31 (62.0)
≥1%	32 (64.0)	19 (38.0)
≥25%	4 (8)	1 (2.0)
≥50%	0 (0)	0 (0)

8.7.1 Characteristics of those experiencing cognitive decline

An exploratory data analysis was conducted to investigate the clinical and demographic characteristics of those who were classified as having cognitive decline. Table 8.10 illustrates the results of this analysis. There were no significant differences between the two groups on any of the demographic, psychological or epilepsy-related variables entered into this exploratory data analysis.

several of the neuropsychological tasks. A letter was also sent to the patient providing feedback on the assessment.

Table 8.10: Characteristics of those classified as having or not having cognitive decline at follow-up

Characteristics	Declined (n=19)	Not declined (n=31)	Diff (95%CI)	*p*-value
Sex (n, %)				
Male	7 (36.8)	12 (38.7)	-1.9 (-27.9, 25.9)	.895
Female	12 (63.2)	19 (61.3)	1.9 (-25.9, 27.9)	
Mean age at FU, yrs (SD, range)	51.11 (14.17, 22-84)	44.10 (15.45, 21-71)	7.01 (-1.77, 15.79)	.115
Mean age at baseline, yrs (SD, range)	45.84 (13.89, 17-78)	38.58 (15.21, 17-65)	7.26 (-1.37, 15.89)	.097
Mean duration, months (SD, range)	62.21 (11.23, 43-85)	65.48 (10.43, 46-84)	-3.27(-9.56, 3.02)	.301
Seizure type at baseline (n, %)				
Partial	15 (78.9)	27 (87.1)	-8.1 (-32.7, 12.7)	-
Generalised	1 (5.3)	3 (9.7)	-4.4 (-21, 16.4)	
Unclassified	3 (15.8)	1 (3.2)	12.6 (-3.5, 35.1)	
Seizure free previous 12 mths (n, %)	13 (68.4)	16 (51.6)	16.8 (-11.7, 41.7)	.242
No of AEDs at FU (n, %)				
0	0 (0)	2 (6.5)	-6.5 (20.9, 11.1)	-
1	15 (78.9)	25 (80.6)	-1.7 (-27.1, 20.3)	
2	4 (21.1)	4 (12.9)	8.1 (-12.7, 32.7)	
TPM at FU (n, %)	5 (26.3)	5 (16.1)	10.2 (-12.4, 35.5)	.382
Baseline abnormal imaging/neurological disorder (n, %)	7 (36.8)	8 (25.8)	11.0 (-14.6, 37.5)	.409
Co-morbidities at FU (n, %)	8 (42.1)	12 (38.7)	3.4 (-23.5, 30.9)	.812
Classified as impaired at baseline (n, %)	9 (47.4)	19 (61.3)	-13.9 (-40.4, 14.2)	.336
Median education at FU, yrs (25th-75th centiles)	12 (11-18)	12 (11-15)	0 (-1, 2)	.812
Mean tension at FU (25th-75th centiles)	30.56 (16.67-44.44)	22.22 (13.89-36.11)	-8.33 (-2.78, 19.44)	.136
Employment status at FU (n, %)				
Employed/FT education	8 (42.1)	18 (58.1)	-16.0 (-41.9, 12.5)	.273
Unemployed/retired	11 (57.9)	13 (41.9)	16.0 (-12.5, 41.9)	

8.8 Summary

Fifty people with epilepsy were assessed as part of this follow-up study. They were assessed, on average, five years after their baseline assessment (minimum 3 ½ years, maximum 7 years). The majority were females with an average age of 46 years. The majority had partial epilepsy and were well-controlled on monotherapy. The majority had not had any seizures for at least the 12 months prior to the assessment. These patients were comparable to the group of patients who were eligible to take part but did not in terms of their demographic (age and gender) and clinical characteristics (epilepsy type) at baseline. However, they did have more years of formal education. Despite having more years of formal education at baseline, they were comparable in terms of their neuropsychological test performance at baseline and 12 months. This suggests that there was not a bias for those experiencing more cognitive problems during SANAD to return to the study. Equally, there is no evidence to suggest that those who experienced more cognitive problems during the course of SANAD did not want to take part.

After an average of five years, their performance was poorer compared with baseline, on measures of memory (immediate and delayed Rey Auditory Verbal Learning Test) and visual reaction time (dominant and non-dominant hand). There were also trends for poorer performance on other memory measures (serial recognition of words) and information processing (Adult Memory and Information Processing Battery and CVST). Interestingly, there were improvements on the serial recognition of figures task. Visual inspection of the proportions of people who fell into the different classifications of the Stroop, also suggested improvements on this task from baseline. The remaining measures had stable performance from baseline. Taking into account baseline scores, most declines were again seen for the Rey Auditory Verbal Learning Test, visual reaction time measures and information processing on the CVST. But these declines were subtle and for most measures, declines were on average less than 5% from baseline.

There were no differences in the amount of cognitive change experienced between those who continued to have seizures and those who had been seizure free for at least the previous 12 months. Similarly, there were no differences between those who had other medical diagnoses

during the 12 month and follow-up interval or those who had a previousor current neurological disorder or known cerebral pathology at baseline. There was only a trend for years of education to be associated with change on delayed story recall and duration of epilepsy with simultaneous recognition of words. Age was significantly associated with cognitive change on the psychomotor speed subtests of the Adult Memory and Information Processing Battery and symptoms of tension were associated with cognitive change the three psychomotor speed variables (tapping with both hands and psychomotor speed of AMIPB). Having a poorer baseline performance was associated with most cognitive decline on five of the measures.

In terms of mood, people with epilepsy reported experiencing fewer symptoms of anxiety at the time of the follow-up assessment but there were no other statistically significant changes in mood. On the ABNAS self-report measure, patients reported experiencing more cognitive problems but these were not statistically significant changes.

At an individual-level, 38% of patients were classified as having cognitive decline, when cognitive decline was defined as having a follow-up score more than 2 SD below baseline. However, there were no differences in demographic, epilepsy or psychological related variables between those who were classified as having or not having cognitive decline. These results and the ones from the previous chapters will be discussed in Chapter 9.

Chapter 9 Discussion

9.1 Overview of the chapter

This chapter will discuss the results of this research programme, which aimed to explore the natural history of cognitive functioning in people with newly diagnosed epilepsy. There will be a discussion of the three results chapters, which aimed to fulfil the three objectives of this thesis. Each series of results will be considered within the context of the previous literature. Finally, the strengths, limitations, importance and clinical implications of the research will be reviewed and recommendations for future investigation will be proposed.

9.2 The immediate impact of epilepsy

9.2.1 Findings from this research

Cognitive impairments are frequently reported by people with epilepsy, but when these arise in the course of the disorder is an important issue. Many patients attribute their impairments to the side effects of AED medication (International Bureau for Epilepsy, 2004, Carpay *et al.*, 2005, Baker *et al.*, 2008). However, the results of this research suggest that patients with newly diagnosed epilepsy, who are otherwise neurologically normal (on the basis of available evidence), were performing significantly worse than healthy volunteers on 11 of 17 cognitive measures before the start of AED treatment. After adjusting for age, sex and education, these differences persisted for the domains of memory and psychomotor speed. At an individual-level, patients with epilepsy had a higher proportion of abnormal test scores (i.e. an adjusted z-score $\leq$-2.0) across the battery (e.g. on the AMIPB psychomotor speed task 18.4% of people with epilepsy had an abnormal score vs. 2.3% of the healthy volunteers). They were also four times more likely than healthy volunteers to demonstrate cognitive impairment (defined as at least one abnormal test score). Fifty-four per cent were classified as having impairment at baseline compared with 21% of healthy volunteers.

Previous studies have suggested that adults with newly diagnosed epilepsy already demonstrate evidence of cognitive dysfunction, in particular, memory impairments, at the time of diagnosis (Brodie *et al.*, 1987, Smith *et al*, 1987, Kalviainen *et al.*, 1992, 2003, Helmstaedter *et al.*, 1993, 2005, Aikia *et al.*, 1995, 2001, Prevey *et al.*, 1998, Ogunrin *et al.*, 2000, Pulliainen *et al.*, 2000a). The current research, in concordance with these, has shown that cognitive impairments occur in patients without structural brain abnormalities on clinical CT/MRI, before AED treatment and following relatively few seizures. Consistent with the previous literature, this research found that it was a proportion of patients (54%) that were most affected. In a series of studies by Kalviainen and colleagues, approximately 30-56% of patients were found to have mild memory and attention problems (Kalviainen *et al.*, 1992, Aikia *et al.*, 1995, 2001).

9.2.2 Potential causes of cognitive impairment

Effects of seizures

Some of these studies have suggested a potential role for seizures as a cause of cognitive impairment. Prevey *et al.*, (1998) and Aikia *et al.*, (2001) found greater cognitive impairment to be associated with secondarily generalised seizures. However, in this research programme there were no differences between those with partial, generalised and unclassified seizures across the cognitive measures, except for the psychomotor speed task of the AMIPB; although this finding must be interpreted with caution due to the unequal numbers in the groups. Similarly, there were no differences in seizure type between those with or without cognitive impairments. This supports the findings of Pulliainen *et al.*, (2000a) who also found no differences between those with partial or generalised seizures in 52 adults with newly diagnosed epilepsy.

The observed differences were also not mediated by the frequency of seizure activity. Patients had experienced a median number of nine seizures before the baseline assessment but there were no significant relationships between the total number of seizures or the number of GTCS experienced and any of the neuropsychological test variables. There were no differences in the median number of seizures experienced by those who were or were not

classified as impaired. This was surprising, as previous research has suggested that a larger number of seizures are associated with greater cognitive impairment (e.g. Dodrill, 1986, Vlooswijk *et al.*, 2008); although these studies were not conducted in those who were newly diagnosed. However, those whose first seizure was more recent had poorer scores on a visual recognition memory task and there was a trend for those with a shorter interval since their first seizure to be classified as having impairments at baseline. Helmstaedter *et al.*, (2005) also found shorter duration of untreated epilepsy to be associated with poorer performance but the mechanism underlying this finding was unclear. Whether this reflects greater CNS dysfunction due to a more recent seizure; the effects of an acute psychological reaction to their first seizure or another reason entirely requires further investigation and explanation.

Role of the underlying aetiology

The specific mechanisms leading to cognitive dysfunction at epilepsy onset remain uncertain. As reviewed in Chapter 4, three potential factors are the underlying aetiology, the effects of epileptogenesis or the result of psychological adjustment to epilepsy. The fact that these differences were found after excluding 67 patients with a previous or current neurological disorder and/or abnormal neuroimaging implies that their poorer performance was not a result of their underlying aetiology. This is consistent with studies by Kalviainen *et al.*, (1992) and Aikia *et al.*, (1995) who also found poorer cognitive performance, particularly in attention and memory, in adults with new-onset epilepsy, after excluding those with a known cerebral pathology. Similarly, studies from the paediatric literature have found that children with new-onset idiopathic and cryptogenic epilepsy have generalised cognitive dysfunction at the time of diagnosis (Oostrom *et al.*, 2003, Berg *et al.*, 2005, Hermann *et al.*, 2006a, Bhise *et al.*, 2009). However, some patients in this research programme may have had underlying abnormalities or pathologies that were not detected by these methods. Structural brain abnormalities, such as gliosis, atrophy and reduced grey matter volumes, have been associated with poorer neuropsychological functioning in children with newly diagnosed epilepsy (Hermann *et al.*, 2006a, Byars *et al.*, 2007). Differential relationships between white matter volumes and cognition have also been found between children with idiopathic new-onset epilepsy and healthy first-degree cousin controls (Hermann *et al.*, 2006a). Therefore,

future work should include structural and functional imaging to uncover whether specific neuroabnormalities underlie these cognitive deficits (see section 9.7.1 below).

Role of psychological factors

Oostrom *et al.*, (2003) found that the differences in cognitive functioning between children with newly diagnosed epilepsy and healthy gender-matched classmate controls were not related to their epilepsy characteristics but to the reaction of the child and their parent(s) to the diagnosis of epilepsy. In the current research, patients were also assessed at the time of diagnosis, which is a period of complex psychological adjustment (Chaplin *et al.*, 1992, Kemp *et al.*, 1999). It may be that those who demonstrated most dysfunction had a more pervasive loss of control and a more extensive adjustment process (Velissaris *et al.*, 2007).

Whilst psychological adjustment was not measured formally at baseline [e.g. using measures such as the COPE (Carver *et al.*, 1989) or semi-structured interview (Oostrom *et al.*, 2003)], the POMS was used to assess current mood state and has been employed previously as a measure of psychological adjustment in patients with breast cancer (Taylor *et al.*, 1984, Taylor *et al.*, 1985). There were significant differences between the current mood state of people with epilepsy and healthy volunteers. Patients with epilepsy reported experiencing more mood disturbance, in particular, more symptoms of tension and confusion and less vigour than healthy volunteers. This is not surprising, as there is a significant body of literature that has found epilepsy to be associated with an increased number of psychosocial difficulties (e.g. Jacoby *et al.*, 1996, Baker *et al.*, 1997, Hermann *et al.*, 2000, Gaitatzis *et al.*, 2004, Kanner, 2007). These mood factors were also rated more highly by people with newly diagnosed epilepsy compared with healthy volunteers in a study by Pulliainen *et al.*, (2000b). These difficulties, particularly anxiety and depression, may be a reaction to the onset of epilepsy or reflect a shared pathophysiology (Kanner, 2006). However, consistent with the findings of Pulliainen *et al.*, (2000b), there was no relationship between neuropsychological test variables and current mood state. Self-reported mood states did not differentiate between those who were or were not classified as impaired, suggesting that the observed differences were not mediated by mood disturbance. In addition, the impact of anxiety on test performance was limited during the testing session, as researchers administering the neuropsychological tests

were trained to postpone the assessment in any patient who demonstrated experiencing significant levels of distress based on clinical judgement.

Role of epileptogenesis

In this research programme it appears unlikely that negative psychological adjustment to a diagnosis of epilepsy caused the cognitive impairments observed at epilepsy onset. In support of this, several studies have suggested that cognitive, academic and behavioural problems antedate the first recognised seizure in some children with epilepsy (e.g. Austin *et al.*, 2001, Berg *et al.*, 2005, Hermann *et al.*, 2006a); although this was not found in a study by McNelis *et al.*, (2007). However, the different findings may be due to the measurement of academic problems. McNelis *et al.*, (2007) compared teacher ratings of classroom performance before the first seizure rather than comparing objective measures, such as use of special education services or measure of academic skills (e.g. reading, writing and maths). The existence of these problems before the first seizure implies a possible role for the underlying epileptogenesis (Hermann *et al.*, 2006a, 2008a, 2008b). Epileptogenesis is the process by which a normal neural network becomes a hyperexcitable one that predisposes to recurrent seizures (Badawy *et al.*, 2009a, 2009b). This process may cause cerebral alterations, such as network reorganisation, that impact on cognition. Whilst the results of the current research cannot provide direct evidence in support of this hypothesis, this is an explanation that is worthy of further exploration.

9.2.3 Predictors of cognitive impairment and future outcome

It was surprising that demographic, epilepsy or mood-related variables did not differentiate between those who were or were not classified as impaired. On the basis of the literature reviewed in Chapter 3, differences were expected for seizure type, number of seizures, education and age. The lack of findings may have arisen for several reasons:

- the definition of impairment employed in this research programme (i.e. an abnormal test score on *any* cognitive measure) may have resulted in a heterogeneous group that reduced the likelihood of finding significant differences.

A more conservative criterion, for example, impairment on at least two cognitive measures, may have led to the identification of potential predictive factors;

- they are 'genuine' results and these factors are not associated with cognitive impairment at the time of diagnosis in adults with newly diagnosed epilepsy;
- the groups differed on some other indicator (e.g. socioeconomic status, coping style, quantitative MRI volumetrics, white matter tract integrity, genetic susceptibility) that was not measured in this research. This emphasises the need for further studies to specify the mechanisms underlying these impairments and to identify prognostic factors that are able to predict those who are most 'at risk' of baseline cognitive impairment.

Finally, in the current research, baseline cognitive performance was not related to seizure outcome at 12 months or longer-term follow-up (mean five years). This was unexpected, as it does not support the findings of Aikia *et al.*, (1999b) and others who have suggested early cognitive impairment to be a predictor for intractable epilepsy (Kalviainen *et al.*, 1992, Aikia *et al.*, 1995). Also, it does not support results from the Multicentre study of Early Epilepsy and Single Seizures (MESS), which found that individuals who had recurrent seizures throughout a four-year follow-up period, had poorer baseline quality of life outcomes (on domains of physical, cognitive, psychological and social functioning) compared with those who only ever had a single seizure (Jacoby *et al.*, in preparation). Whilst the outcomes of the MESS study were subjective, baseline differences, particularly in ratings of anxiety and depression, suggest that these may be precursors to epilepsy or reflect common underlying susceptibilities.

However, this may reflect how cognitive impairment was classified in this research programme and the definition of seizure outcome employed (i.e. at 12 months: immediate 12 month remission vs. any seizure in the previous 12 months; at five years: any seizure in the last 12 months vs. seizure free for the previous 12 months). In the study by Aikia *et al.*, (1999b), it was presence of verbal memory impairment (i.e. on immediate recall and delayed recognition of a word list) that was a predictor of poor two year seizure outcome (defined as more than one generalised seizure or more than four partial seizures during one year), along

with presence of a spike focus in EEG; complex partial or mixed seizure type; remote symptomatic aetiology and age at time of diagnosis. Therefore, it is possible that a different definition of cognitive impairment or a consideration of *specific* cognitive domains or cognitive measures (e.g. measures of memory functioning) may have identified prognostic factors. Additionally, those who only had one seizure in the previous 12 months were classified as being in the active epilepsy group, which means this group could comprise those who had frequent, daily seizures and those who may have had only one seizure in the previous year. This heterogeneity of epilepsy frequency may have led to the failure to find significant relationships. Interestingly, baseline cognitive impairment was also not related to the experience of abnormal test performance at 12 months or experience of cognitive decline at five years. Again, this finding may reflect the definition of impairment employed in this particular research programme or may provide support for Huang *et al.,* (2005) who found that those with abnormal scores at baseline testing had significant improvement in overall cognition scores, short-term memory and semantic fluency after three years. Those who were in the normally functioning group at baseline had no significant change.

9.2.4 Summary

Overall, the results of this part of the thesis suggest that, as a group, people with epilepsy are already cognitively compromised at the time of diagnosis. Although the mechanisms underlying these impairments cannot be ascertained; it is speculated that this is most likely due to the result of the epileptic process and/or an unidentified neurobiological abnormality[10]. The next section will discuss how cognitive functioning changed over the next 12 months in comparison with the healthy volunteer group.

[10] However, the limitations of the research may also account for the poorer cognitive performance of people with epilepsy, in particular, the composition of the two groups and effects of subclinical epileptiform discharges. This will be discussed in section 9.5.

9.3 The shorter term impact of epilepsy and its treatment

9.3.1 Findings from this research

How these baseline cognitive impairments develop and progress after the start of AED treatment is also an important issue. In this research, the cognitive functioning of people with epilepsy after the first 12 months of treatment was compared with a healthy volunteer control group, statistically controlling for confounding factors such as practice effects, regression to the mean, baseline performance, age, sex and education. People with epilepsy performed significantly worse than expected on 12 of the 15 neuropsychological test measures. The cognitive domains most affected were psychomotor speed, higher executive functioning and memory. At an individual-level, 42% of patients had abnormal scores on the VRT task with the non-dominant hand and 38% had abnormal scores on the equivalent task with the dominant hand. More than 20% of patients also had abnormal test scores on other psychomotor speed measures (finger tapping with the non-dominant hand and psychomotor speed task of the AMIPB) and a measure of higher executive functioning (verbal fluency). Eighty-five per cent of patients had at least one abnormal test score (i.e. an adjusted z-score ≤-2.0) and 31.3% had an abnormal score on at least a quarter of the cognitive measures.

Performing worse than expected may reflect absolute cognitive decline or reflect a lack of 'normal' improvement in cognitive performance (i.e. practice effects). The results of this research programme support the recent work of Hermann *et al.*, (2006b) who, using the same standardised regression-based change techniques, showed that people with chronic TLE had a different cognitive trajectory to control subjects over a four-year period, which was mainly characterised by a lack of practice effects. Consistent with the results of the current research, bilateral motor speed and memory functioning were the domains most affected in their longitudinal study. Similarly, Andersson-Roswall *et al.*, (2004) and Dodrill (2002) also found a lack of practice effects in people with epilepsy in their longitudinal studies. Andersson-Roswall *et al.*, (2004) suggested that a lack of practice effect may reflect a deficit or impaired capacity for learning from prior exposure to the initial testing experience.

The design of this research programme cannot ascertain the causes and mechanism underlying the different cognitive trajectory, as in this programme it is impossible to separate out the effects of treatment from the effects of epilepsy (e.g. the underlying aetiology, epileptic process and seizures). However, it is plausible that AED treatment is contributing to the poorer than expected performance. Several RCTs investigating the cognitive side effects of AEDs, involving both healthy volunteers and people with newly diagnosed epilepsy, have demonstrated a lack of practice effects after the administration of AED medication (Smith *et al.*, 1987, Pulliainen & Jokelainen, 1994, Prevey *et al.*, 1996, Dodrill *et al.*, 1999, Salinsky *et al*, 2004, 2005). The authors of these studies suggested that a lack of practice effects may be the first indicator of an AED effect. In the randomised clinical trial undertaken by Pulliainen and Jokelainen (1994), an untreated healthy control group demonstrated practice effects for 42% of variables but only 17% of variables improved for people with epilepsy after they started treatment with either carbamazepine or phenytoin. In a healthy volunteer study by Salinsky *et al.*, (2004), healthy volunteers declined on 25% of variables relative to an untreated reference group after the start of AED treatment and consistent with the current research, these variables mainly assessed motor speed. Psychomotor speed, along with attention, vigilance and mental speed have been shown to be vulnerable to the effects of AEDs (e.g. Loring & Meador, 2001, Aldenkamp *et al.*, 2003). This is because they work by decreasing neuronal irritability and suppressing epileptiform discharges but this reduction in neuronal excitability can lead to their cognitive side effects (e.g. Motamedi & Meador, 2003, 2004, Loring *et al.*, 2007).

In this research programme, the differential side effects of AEDs could not be assessed due to a lack of adequate power. However, there was a brief consideration of the effects of topiramate. Topiramate was the most commonly prescribed AED at the time of the 12 month assessment, taken by 23.8% of patients. Topiramate is also associated with a more negative cognitive profile compared with other newer AEDs, particularly for the measures most affected in this research (i.e. verbal memory, psychomotor speed and verbal fluency) (Martin *et al.*, 1999, Aldenkamp *et al.*, 2000, Meador *et al.*, 2003, 2005, Fritz *et al.*, 2005, Salinsky *et al.*, 2005, Blum *et al.*, 2006). Therefore, it was expected that a higher proportion of those in the abnormally performing group (i.e. at least one abnormal test score) compared with the

performing as expected group would be taking topiramate. This hypothesis was not supported. However, this may reflect the fact that those who had either remained on, or changed to, topiramate at the time of 12 month assessment were possibly well-controlled and had not experienced serious adverse advents on the drug or they would have withdrawn during the course of SANAD.

It was surprising that after taking into account practice effects, regression to the mean, baseline performance, age, sex and education, people with epilepsy performed significantly better than expected on the Computerised Visual Search Task, especially, as they experienced declines for another information processing task (AMIPB). Whether this finding reflects a genuine improvement in performance on this particular task; is a statistical artefact related to the construction of the standardised regression-based z-scores; or is due to another reason is something that would require further investigation by replication in another study.

9.3.2 Factors associated with poorer than expected performance

As discussed above, the causes of the differing cognitive trajectory could not be determined; however, the factors associated with obtaining poorer than expected performance were investigated in the analyses.

Effects of seizures

Patients had experienced a median number of three seizures since the baseline assessment and the majority had not experienced any GTCS. The number of seizures was not related to any of the neuropsychological test variables and there were no differences in cognitive test scores between those who achieved an immediate 12 month remission and those that continued to have seizures. These findings are at odds with the significant body of literature suggesting greater cognitive impairment with recurrent seizures (Rodin, 1968, Seidenberg *et al.*, 1981, Dodrill, 1986, Upton & Thompson, 1997, Meador, 2002). However, this finding is in concordance with the findings of Dodrill (2002) who found no relationships between the number of partial seizures and cognitive change.

Whilst not statistically significant, there was a trend for verbal recognition memory to be negatively associated with number of GTCS and there was a trend for those who had experienced a higher number of tonic-clonic seizures to be in the abnormally performing group. Similarly, those with generalised epilepsy also performed worse than those with partial and unclassified epilepsy on immediate verbal recall of a list learning task and worse than those with partial epilepsy on a serial recognition of words task but performed better on the psychomotor speed test of the AMIPB; although these results should be interpreted with caution due to the unequal numbers in the three groups. This supports studies that have found generalised seizures to be associated with greater cognitive impairment (Thompson & Duncan, 2005, Piazzini *et al.*, 2006). However, there were no differences on the remainder of measures and there were no differences in seizure type between those who were or were not classified as having abnormal test performance. This supports others who have found that there are no differences between those who experience partial and generalised seizures (O'Leary *et al.*, 1983, Pulliainen *et al.*, 2000a).

An unexpected finding was the trend towards those who had achieved a 12 month seizure remission to perform worse on a verbal fluency task. It is unclear what mechanisms might underlie this, albeit non-significant, finding but it may possibly be mediated by other factors, such as the characteristics of those who had achieved an immediate 12 month remission (e.g. their medication or other demographic factors).

Effects of mood

Current mood state was significantly associated with poorer than expected levels of performance for several measures, particularly, those measuring psychomotor speed. At 12 months people with epilepsy reported significantly fewer symptoms of tension compared with baseline, which may suggest a positive psychological adjustment to their diagnosis of epilepsy (e.g. Velissaris *et al.*, 2007). Despite this improvement, people with epilepsy still reported significantly more symptoms of tension, depression, anger, vigour and confusion than the healthy volunteers. Their current mood state was significantly associated with several of the neuropsychological test variables. Psychomotor speed tasks, especially the psychomotor speed task of the AMIPB and the visual reaction time tasks, were associated with symptoms

of tension, depression, anger and a lack of vigour. This is consistent with the general neuropsychological literature that has found mood disturbance to interfere with performance on neuropsychological tasks, particularly timed tasks (Reitan & Wolfson, 1997, Paradiso *et al.*, 2001, Douglas & Porter, 2009). However, current mood state, apart from symptoms of confusion (discussed in section 9.3.3 below), were not different between those who were or were not classified as having more abnormal test performance.

9.3.3 Characteristics of those with poorer than expected outcomes

Similar to the findings at baseline, it was interesting that demographic, epilepsy or mood-related variables did not differentiate between those who were or were not classified as having abnormal performance; although there were trends for number of tonic-clonic seizures (as discussed in section 9.3.2 above), education and self-reported symptoms of confusion. The lack of findings at 12 months may have arisen for the same reasons as discussed in section 9.2.3. Firstly, the definition of abnormal test performance employed in this research programme may be too lenient, which may explain why 85% of patients in this thesis had abnormal test performance compared with 20-25% in the study by Hermann *et al.*, (2006b). Secondly, patients may not differ on these factors but on some other indicator that was not measured.

In the study by Hermann *et al.*, (2006b) abnormalities in baseline quantitative MRI volumetrics; lower baseline IQ; longer duration of epilepsy and older age predicted risk of poor cognitive prognosis. In this current research, neither age at assessment nor age at first seizure differentiated the two groups. Previous research has suggested that those with an early age of onset may have poorer cognitive outcomes (e.g. Dikmen *et al.*, 1975, O'Leary *et al.*, 1983, Schoenfeld *et al.*, 1999, Aikia *et al.*, 2001, Meador, 2002, van Mil *et al.*, 2008). However, the lack of an age-effect in this research probably reflects the fact that patients had adult-onset epilepsy with a mean age of 29 years at first seizure. As this seizure would have occurred within the context of a developed brain, this would have avoided the consequences of disruption to normal developmental processes, such as synaptogenesis and myelination, that are associated with an early age of onset (Anderson, 2001, Brown, 2006). However, more severe disruption can sometimes occur in adulthood due to the lack of plasticity and potential

for compensation or cerebral and functional reorganisation (e.g. Muller *et al.*, 1998). As discussed in section 9.2.3, baseline cognitive impairment was not associated with 12 month cognitive outcome and possible explanations for this have been proposed. The finding of more abnormal baseline quantitative MRI volumetrics to be associated with poorer cognitive outcome cannot be directly compared with this results from this research. However, those with an underlying aetiology or abnormal neuroimaging on CT/MRI were not more likely to be in the abnormally performing group.

There was a trend for those with lower years of education at baseline to be in the abnormally performing group and those with higher levels of education to be in the 'as expected' group. This is in concordance with the findings from a longitudinal study by Piazzini *et al.*, (2006) who also found lower levels of education to be associated with cognitive decline after five years in adults with TLE. It also lends support to the findings from cross-sectional studies that have found that higher levels of education slow the rate of decline in those with longer duration of epilepsy (Jokeit & Ebner, 1999, Oyegbile *et al.*, 2004). Higher levels of education may act as a proxy marker for cognitive reserve, which is the ability to process tasks in a more efficient manner (possibly through the differential recruitment of brain networks), so that greater brain damage can be sustained before a functional deficit is demonstrated (Stern, 2002).

The trend towards those with higher symptoms of self-reported confusion at 12 months to be in the abnormally performing group most probably reflects the nature of this POMS sub-scale. This sub-scale measures feelings of bewilderment and muddleheadedness and comprises items such as 'being unable to concentrate', 'forgetful' and 'confused' (McNair *et al.*, 1992). Therefore, it is unsurprising that these characteristics are found in those who have a lower than expected cognitive performance.

9.3.4 Summary

Overall, the results of this analysis suggest that, as a group, people with newly diagnosed epilepsy have a different pattern of cognitive performance than a non-epilepsy healthy volunteer control group after 12 months of treatment. The majority of patients had poorer than expected scores on at least one of the cognitive measures, after correcting for practice

effects, regression to the mean, age, sex and education. Whilst this research programme cannot specify the mechanisms underlying this differing cognitive trajectory, AED treatment is the most likely explanation[11]. Current mood state was associated with poorer than expected performance, particularly for psychomotor speed measures. There were no differences in demographic, epilepsy or mood-related variables between those who were or were not classified as having abnormal performance; although there were trends for increased number of tonic-clonic seizures; lower levels of education and more feelings of confusion to be associated with poorer performance. The next section will discuss how cognitive functioning changed from baseline in a proportion of patients who were followed-up after an average of five years.

9.4 The longer term impact of epilepsy and its treatment

9.4.1 Findings from this research

Despite the importance of understanding how cognition changes over time in people with epilepsy, relatively few longitudinal studies have been undertaken to investigate this issue (Arieff & Yacorzynski, 1942, Rodin, 1968, Seidenberg *et al.*, 1981, Dodrill & Wilensky, 1990, 1992, Kalska, 1991, Selwa, *et al.*, 1994, Holmes *et al.*, 1998, Helmstaedter *et al.*, 2000, 2003, Aikia *et al.*, 2001, Bjørnæs *et al.*, 2001, Dodrill, 2002). Of these, only one has included those with newly diagnosed epilepsy (Aikia *et al.*, 2001).

This research programme has shown that after a mean of 64 months since baseline assessment, the majority of cognitive measures remained stable but there were significant declines for four of the 16 measures. Measures affected were those assessing psychomotor speed and immediate and delayed verbal recall. However, the magnitude of this change was subtle, representing a 10-15% change from baseline. At an individual-level, approximately 10% of patients had scores that were more than 2SD below their baseline performance for immediate recall on a list learning task and on a VRT task with the dominant hand. A total of

[11]However, as at baseline, the limitations of the research (see section 9.5), particularly the composition of the two groups may also account for their poorer than expected cognitive performance.

38% of patients were classified as experiencing cognitive decline (i.e. at least one cognitive test score >2SD below baseline).

The relatively stable findings must be interpreted with caution due to the lack of a control group (the implications of which are discussed in more detail in section 9.5). However, the findings of decline for some measures, particularly verbal memory, in the current research are inconsistent with the previous study by Aikia *et al.*, (2001) and a previous published abstract by Aikia *et al.*, (1999a). Aikia *et al.*, (1999a) reported no significant declines on measures of verbal ability, verbal learning and memory, attention and flexibility of mental processing in 58 untreated patients with newly diagnosed epilepsy after five years. They also found statistically significant (although small) improvements in several neuropsychological measures due to normal practice effects; although, they did not report which measures improved. Aikia *et al.*, (2001) found no deteriorations and some improvements (delayed recall of a list learning task) in verbal memory in 20 adults with newly diagnosed TLE after five years.

Possible explanations for the differences between the current research and these prior studies include the characteristics of the patients with epilepsy[12]. Firstly, in the study by Aikia *et al.*, (2001) all patients were seizure free. In the abstract by Aikia *et al.*, (1999a) all patients were either seizure free or had only occasional seizures. In this research programme, only 58% of patients were seizure free for at least the previous 12 months at five year follow-up. Six percent of patients reported having seizures every day, six per cent at least once a week and a further 24% reported having seizures at least once a month. The higher frequency of seizures reported by patients in this research may have contributed to their observed declines on some measures or may reflect that they had a more severe form of epilepsy, which may be associated with more cognitive impairment. However, there were no differences on any of the neuropsychological test variables between those who had been seizure free for the previous 12 months and those that continued to have recurrent seizures. Similarly, the proportions of people who were seizure free for the previous 12 months did not differentiate those that did or

[12] Comparisons between this current research and the study by Aikia *et al.*, (2001) should be made with caution, as all their patients had newly diagnosed TLE. In this research, while the majority had partial epilepsy, the localisation was mixed. For the majority (52%), localisation was not specified and only 30% had been diagnosed with TLE.

did not experience cognitive decline [as discussed previously, this may represent how seizure outcome was classified (see section 9.2.3)].

Secondly, whilst the specific AEDs taken were not reported in either prior study, Aikia and colleagues described patients as 'adequately treated' in the abstract (1999a) and patients were treated with monotherapy in the published study (2001). In the current research, 16% of patients were being treated with polytherapy (maximum two drugs) and 20% were taking topiramate. Both are known risk factors for cognitive impairment (e.g. Kwan & Brodie, 2001, Aldenkamp *et al.*, 2003, Mula & Trimble, 2009). However, as at 12 months, there was no relationship between taking topiramate and cognitive decline. Again, this possibly reflects the fact that those continuing to take topiramate at five year follow-up are more likely to be able to tolerate this drug. A comparison of the number of drugs taken at follow-up in these two groups was too small for statistical analysis; however, the difference in proportions and their respective 95% confidence intervals, suggested that there were no differences.

Thirdly, the differences in findings could be related to symptoms of mood disturbance. In this research, current mood state, particularly levels of tension, was associated with measures of psychomotor speed (finger tapping task with the dominant and non-dominant hand and psychomotor speed task of the AMIPB). As discussed in relation to the 12 month results (see section 9.3.2), mood disturbance may interfere with neuropsychological test performance (Reitan & Wolfson, 1997, Paradiso *et al.*, 2001, Douglas & Porter, 2009). However, the current mood state of patients with newly diagnosed epilepsy in the previous studies was not reported.

Fourthly, the patients in this research programme had a mean age of 46 years at five year follow-up compared with 38 years in the study by Aikia *et al.*, (2001). Whilst, this difference may only represent an average of 8 years, older age was associated with poorer performance on the psychomotor speed task of the AMIPB in this research; although there were no differences in age between those who did or did not have cognitive decline. Older age has been associated with poorer performance on this particular task (Coughlan & Hallows, 1985) and declines in processing speed, memory and executive functions are known to decline from early adulthood from the normal ageing literature (Deary *et al.*, 2009). Therefore, it is possible

that the older age of this cohort may have contributed to the memory and psychomotor speed declines observed.

Finally, the inconsistencies may also reflect differing levels of education in the studies. The patients included in this research programme had higher levels of education than those involved in the study by Aikia *et al.*, (2001) (12 years vs. 9 years). They also represented a high functioning group with 18% having a degree or higher qualification. This figure is slightly higher than the proportion of the UK population of working age who hold a degree (16.3%) (Office for National Statistics, 2003). The 50 patients who took part in the neuropsychology follow-up study also had higher levels of education than those who were eligible but did not take part. Whilst years of education was not significantly associated with any of the neuropsychological test variables in this research, Pai & Tsai (2005) found that those with high education deteriorated in mental manipulation and those with low education improved in verbal memory but deteriorated in attention over a 12 month period. However, this seems paradoxical and is at odds with with the cerebral/cognitive reserve hypothesis theory discussed in section 9.3.3.

9.4.2 Predictors of cognitive outcome

A failure to find factors that differentiated those who were classified as experiencing cognitive decline from those that were not is consistent with the findings from the previous time-points. The possible explanations for this have been reported in those sections and, for brevity, will not be repeated here. However, the proportion of patients experiencing cognitive decline (38%) is in concordance with other longitudinal studies investigating cognitive change in people with epilepsy. Arieff & Yacorzynski (1942) identified 37% of patients with symptomatic epilepsy who significantly declined in intellectual functioning. Helmstaedter *et al.*, (2000) also identified 37% of patients with TLE who declined in memory functioning after a mean of 56 months. Similarly, Kalska (1991) found that 64-89% of people with epilepsy remained unchanged on the various tasks after an average of 10 years.

9.4.3 Summary

After a mean of five years, people with newly diagnosed epilepsy demonstrated relatively stable measures of cognitive performance across a comprehensive neuropsychological test battery. However, there were statistically significant (although subtle) declines on measures of verbal memory and psychomotor speed. Cognitive changes were most associated with higher levels of tension and older age was significantly associated with poorer performance on a measure of psychomotor speed. A proportion of patients seemed to demonstrate most declines; however, the characteristics of this group could not be identified. The next section will discuss the limitations of this research.

9.5 Limitations of this research

All of the above findings must be interpreted within the context of the study limitations. Many of these are associated with the healthy volunteer control group.

9.5.1 Healthy volunteer group

Firstly, the healthy volunteers were not assessed at the same time as the people with epilepsy due to resource limitations. They were recruited between three to eight years later. In the SANAD Neuropsychology study the people with epilepsy served as their own controls. However, it was felt that a healthy control group was necessary to inform on the impact of epilepsy at the time of diagnosis and to provide an estimate of the test-retest effects of the neuropsychological test battery. The later data collection, whilst not ideal, was felt to be a necessary compromise to having no control group for the first 12 months, for the purposes of this thesis.

Secondly, as the healthy volunteers were collected at a later time point, there was no control group involved in the neuropsychology follow-up study. As discussed in Chapter 4, a lack of a comparison control group was identified as a methodological shortfall of previous longitudinal studies of this type. This is because the neuropsychological test performance of people with epilepsy has been characterised by 'abnormal' functioning rather than abject deterioration

(Dodrill, 2002, Andersson-Roswall *et al.*, 2004, Hermann *et al.*, 2006b, Piazzini *et al.*, 2006, Griffith *et al.*, 2007). Therefore, the stable performance on the majority of measures identified in Chapter 8 needs to be interpreted with caution, especially in light of the results in Chapter 7, which supports the idea of a differing cognitive trajectory. Additionally, again due to resource limitations (financial and time), the healthy volunteers were not assessed at three months. However, the findings of a lack of practice effect at 12 months are even more significant, as this implies that people with epilepsy did not benefit from their additional exposure to the neuropsychological test material highlighting poorer learning and memory ability.

Thirdly, the control group assessed as part of this research programme may not have been the best possible control group. Whilst, healthy volunteers were matched for age and sex at baseline, they had significantly higher levels of education. Education is correlated with IQ (Smith *et al.*, 1987), which implies that the healthy volunteer group were more intelligent possibly accounting for their superior performance at baseline and 12 month follow-up. However, education was adjusted for in the statistical analysis at both time-points. Additionally, socio-economic status of the patients involved in the SANAD Neuropsychology study was not recorded, so it was not possible to match the healthy volunteers for this. A preferred control group would have been friends or family of the people with epilepsy (possibly siblings or first-degree cousins), which would have controlled for sociodemographic characteristics. Two interesting additional control groups could also have been:

- a small control group comprising people who had been diagnosed with epilepsy but for whatever reason had made a decision not to be treated with AEDs (e.g. women of childbearing age). This would allow for a comparison of the absolute effects of AED treatment separate to the effects of epilepsy. People with single seizures have been used as a reference group in other previous AED studies (Kalviainen *et al.*, 1995; 2003, Aikia *et al.*, 2006a). If those who were untreated had similar cognitive trajectories to those who were treated this would imply that the abnormal cognitive trajectory observed at 12 months was related to the underlying epileptic process. However, practically, as part of this research, these

individuals may have been difficult to identify and of course it would be unethical to randomise people to this group.

- a control group comprising people with a recent diagnosis of another chronic condition, for example asthma or diabetes mellitus. This would enable a direct assessment of the contribution of psychological adjustment to baseline cognitive impairment. These controls have been recruited in studies of children with epilepsy (e.g. Williams *et al.*, 1998, McNelis *et al.*, 2007) but to the best of my knowledge, there is no similar study in adults. This would be a useful and interesting endeavour, especially, as psychological adjustment to a diagnosis of epilepsy was not formally assessed in this research. However, epilepsy may be associated with a more negative reaction than these other conditions due to the felt stigma associated with the condition (Scambler, 1989, Jacoby, 2002, Jacoby & Austin, 2007).

9.5.2 People with epilepsy

There are also limitations associated with the epilepsy group. Firstly, the people with epilepsy involved in this research programme represent a heterogeneous group. They had differing aetiologies, seizure types and syndromes. This means that caution should be made when drawing conclusions from this group to particular individuals. Previous research has suggested that different syndromes are associated with different cognitive profiles, for example, memory deficits found in people with temporal lobe epilepsy (e.g. Baxendale *et al.*, 1998, Hermann *et al.*, 1997) and executive function deficits in people with juvenile myoclonic epilepsy (e.g. Hommet *et al.*, 2006, Piazzini *et al.*, 2008, Iqbal *et al.*, 2009). This may be the reason why generalised cognitive deficits were found at baseline and may offer a potential explanation as to why none of the epilepsy-related characteristics were associated with cognitive impairment. One potential avenue for future research would be to recruit specific epilepsy syndromes at the time of diagnosis and follow these more homogenous groups over the course of the disorder. This would also make a significant contribution to the literature, as the majority of research has been undertaken in people with TLE, mainly because it is the most common type of epilepsy; it is often refractory to medication and is associated with

cognitive morbidity. There is a lack of knowledge on the natural history of other epilepsy syndromes.

Secondly, the participants in this research programme may also reflect a selection bias. Whilst, the SANAD trial was a randomised clinical trial, the SANAD Neuropsychology trial was not. It was a prospective, longitudinal study that was undertaken as part of the larger trial and people with newly diagnosed epilepsy from the 11 hospital centres were invited to take part in the study. The numbers and characteristics of SANAD patients who were approached to take part but did not consent, were unfortunately not recorded, therefore, a comparison of their characteristics cannot be made. It is possible that those who felt they already had cognitive problems at baseline were more willing to take part.

Similarly, selection bias may have occurred at the 12 month or longer-term follow-up assessments. There was a large loss to follow-up (66% completed 12 month assessment and 23% of the original sample at five-year follow-up). Those that remained in the study may have been those who were concerned about cognitive problems and so wanted neuropsychological assessment (particularly as a large proportion of them were on topiramate), or those who felt that their epilepsy did not have a significant impact on their cognitive functioning may not have felt that the study was relevant to them and dropped-out. This is plausible as one of the most common reasons people gave for not wanting to take part in the follow-up study was a lack of time, mainly due to work commitments. This implies that these patients may have had better cognitive outcomes as their epilepsy was not impacting on their occupational functioning. Equally, those who found the neuropsychological tasks most challenging, or were most impaired, may not have wanted to take part. Ill health was cited as a reason for not wanting to take part by three people and an assessment could not be carried out for one person because of their severe seizures.

However, this is unlikely to have affected the findings because at 12 months, there were no differences in demographic characteristics of those who did or did not take part. There were no differences on the neuropsychological measures except for those who remained in the study had significantly poorer baseline finger tapping scores with the non-dominant hand and there were trends for poorer performance on the finger tapping task with the dominant-hand

and the visual reaction time tasks with the non-dominant hand. At longer-term follow-up, those who took part had significantly more years of formal education than those who were eligible but did not take part. There were no differences on any of the baseline or 12 month measures, except a trend towards those who did not take part to have lower scores on the information processing and psychomotor speed sub-tests of the AMIPB. Therefore, at these follow-up times, patients seemed to be representative of the original sample.

9.5.3 Study design

There are also limitations with the design of the research that affect the conclusions that can be made. Not only was the SANAD Neuropsychology study underpowered to detect differential drug effects, the neuropsychology follow-up study fell short of recruiting the 95 patients that were required in the power calculation and so the lack of cognitive change from baseline may reflect insufficient power. However, this follow-up study assessed 50 patients, which is more than half of the previous longitudinal studies in this area. Recruitment of patients into the follow-up study was challenging. Sixty-nine percent of approached patients responded to the invitation letter but only 41% wanted to take part. There was no response from 31% and 28% refused. The majority of those who responded but refused did not give a reason, but of those who did, the most common was a lack of time due to family or work commitments or ill health. Half-way through the recruitment period, a newsletter was produced to try and increase the response rate. This tried to emphasise the importance of the research and the progress in data collection so far.

In addition, as the neuropsychology follow-up study was designed after the SANAD Neuropsychology study had finished, patients were not told prospectively to record their number of seizures during the interval since their 12 month assessment. Therefore, the number of lifetime seizures could not be included in the longer term analysis. Previous research has suggested that a higher lifetime number of seizures are associated with cognitive decline (Dodrill, 1986, Vlooswijk *et al.*, 2008) and several authors have recommended that the number of seizures is incorporated into analyses (Dodrill, 2002, Mula & Trimble, 2009). However, these were recorded during the first 12 months and patients were

asked about their seizure frequency in a semi-structured interview prior to their follow-up assessment.

Not only is the thesis limited in drawing conclusions about the effect of number of seizures on cognitive change, it cannot rule out the negative effects of interictal epileptiform EEG discharges. It is possible that the cognitive dysfunction observed may have been the result of transitory cognitive impairment (Aarts *et al.*, 1984, Binnie *et al.*, 1987, Aldenkamp, 1997, Binnie, 2001, Aldenkamp & Arends, 2004). However, it would have been expensive and impractical to carry out EEG and video-monitoring at the time of neuropsychological assessment as part of this research programme.

Finally, the presence of structural pathology was based on the results of routine clinical brain imaging (CT/MRI) that were undertaken within three months of randomisation. In the analysis of the results at baseline, those with an abnormal scan were excluded from this analysis but some patients may have had abnormalities that were undetected, which may have contributed to their poorer cognitive functioning.

9.5.4 An ideal study

All research studies are constrained by resource limitations and the majority of the limitations of this thesis reflect a lack of time and money. In an ideal world, this research programme would have been designed to include an age, sex and education-matched control group from the beginning comprised of siblings or first-degree cousins of the people with epilepsy. There would also be two other control groups comprising people with a chronic illness and a small group of those who have been diagnosed with epilepsy but were untreated. They would be assessed at the same fixed time points using a comprehensive neuropsychological battery and would undergo structural (e.g. quantitative MRI) and functional imaging (e.g. fMRI, diffusion tensor imaging) at baseline and follow-up to identify whether specific neuroabnormalities underlie their differences. EEG and video-monitoring would be undertaken whilst patients perform the neuropsychological tests to ensure they are not experiencing subclinical epileptiform EEG discharges and transitory cognitive impairment. Participants would be followed-up for a longer period of time (>10 years) and with more frequent interim

assessments to more accurately chart their cognitive trajectories. Clinical information, such as number of seizures, number of generalised tonic-clonic seizures and medication changes and dosages would be collected to be used as covariates in analyses. Ideally, the study would only include those with one type of epilepsy, for example, unilateral TLE (to reduce heterogeneity effects and to control for localisation of the epileptogenic focus) or those with idiopathic generalised epilepsy (to control for the effects of the underlying lesion or other identifiable pathology).

9.6 Importance of this research

Despite these methodological shortfalls, this is an important piece of research. Cognitive abilities allow us to process information, which enable us to interact with the world and other people. Cognitive difficulties can impact on day-to-day functioning, academic and occupational achievement, social relationships, psychological well-being and overall quality of life [for a review see Baker *et al.*, (2009), and Mitchell *et al.*, (2010)]. In fact, in this research, people with epilepsy reported experiencing a high number of cognitive problems in their daily lives, particularly in areas of memory (e.g. difficulty remembering names of people; forgetting appointments) and slowing (e.g. takes longer to do day to day things; react too slowly to things that are said) on the ABNAS self-report measure. Therefore, knowledge and understanding of how cognitive functioning is affected and progresses in people with newly diagnosed epilepsy is important in order to inform patients of the risks of cognitive impairment; guide appropriate interventions and ultimately ameliorate its impact on quality life. The importance of this thesis is further highlighted in the strengths and clinical implications discussed below.

9.6.1 Strengths of this research

Firstly, this research contributes to the growing literature that people with epilepsy are already cognitively compromised at the time of epilepsy onset, before the administration of AED medication. Unlike several of the previous studies (e.g. Brodie *et al.*, 1987, Smith *et al.*, 1987, Prevey *et al.*, 1998; Pulliainen *et al.*, 2000a, Ogunrin *et al.*, 2000; Aikia *et al.*, 2001), patients in this research programme were newly diagnosed and had never previously been treated

with AEDs. They had a relatively short duration of untreated epilepsy (median time from first seizure 597 days) and had only experienced a small number of seizures prior to their baseline assessment (median 9 seizures). The research employed a comprehensive neuropsychological test battery with cognitive assessments chosen on the basis of their reliability, validity and previous use in people with epilepsy. By finding that patients demonstrate cognitive impairments, even after excluding those with a known cerebral pathology or previous/current neurological disorder, it adds to the debate about what factors might be causing these impairments. The failure to find a relationship with mood suggests that it is not the result of psychological adjustment factors, and imply that one of the main causes may be the underlying epileptogenesis or epileptic process. Gaining an understanding of these mechanisms is worthy of future research.

Secondly, using standardised regression-based change score techniques, the research has shown that people with newly diagnosed epilepsy have a different cognitive trajectory compared with a comparison healthy volunteer group after 12 months of AED treatment. As discussed in Chapter 5 this statistical technique has several advantages, in particular, it takes into account practice effects, regression to the mean, baseline performance, age, sex and education. Using this technique, people with epilepsy performed more poorly than would be expected based on their age, sex and education for the majority of measures. This supports previous work that suggests that people with epilepsy may have an 'abnormal' test performance that is characterised by differential patterns of learning. Importantly, this thesis represents a shift from studying these trajectories in those with severe, intractable and chronic temporal lobe epilepsy.

Thirdly, 50 patients were followed-up after a mean of five years to assess the longer term impact of epilepsy and treatment. Although, the number of patients recruited for the follow-up assessment was smaller than required from the power calculation, this follow-up study was larger than the majority of previous longitudinal studies in this area. In addition, there has only been one previous peer-reviewed study that has followed-up those with newly diagnosed epilepsy. This study only included 20 patients with left temporal lobe epilepsy and only assessed verbal memory and learning. Despite the absence of a comparison control group for

this time point assessment, the results of these analyses suggested that memory and psychomotor speed measures declined from baseline.

Fourthly, this research programme has suggested that not all people with epilepsy are affected. A proportion of people with epilepsy appear to be most at risk both at baseline (54%) and five year follow-up (38%). While prognostic factors for cognitive impairment could not be identified, this thesis has highlighted the need for further work identifying those most at risk, with a particular focus on structural and functional abnormalities, and a need to screen people for cognitive dysfunction at the time of diagnosis.

9.6.2 Clinical implications

Currently, the National Institute for Health and Clinical Excellence (NICE) guidelines recommend referral for neuropsychological assessment when MRI has identified abnormalities in areas associated with cognitive function; the person with epilepsy is having educational or occupational difficulties and the person with epilepsy complains of memory or other cognitive deficits and/or cognitive decline (Stokes *et al.*, 2004). As the results of this and previous research have suggested that cognitive problems are already present at epilepsy onset, patients should be screened for cognitive dysfunction at the time of diagnosis. This is so that those who are already experiencing cognitive problems can be referred for more comprehensive neuropsychological assessment and appropriate intervention [e.g. retraining or compensation method for attention deficits (Engelberts *et al.*, 2002); external or internal memory strategies such as, diaries, timers, pill boxes or visual imagery and method of loci (Thompson, 1997)]. The guidelines state that awareness of the neuropsychological deficits associated with epilepsy and its treatment may facilitate education, social integration and employment. Therefore, this should be extended to newly diagnosed patients.

Similarly, as this and prior studies have shown that people with epilepsy are at risk of developing further cognitive deficits, particularly in areas of memory functioning, patients should be monitored for cognitive changes. This could take place as part of their annual review by their GP or epilepsy specialist; however, this would require the development of a short screening tool (see section 9.7.3), which could be used to identify those experiencing

cognitive decline who would then be referred for further neuropsychological assessment and intervention. Equally, as mood was found to be associated with poorer than expected performance at 12 months and five year follow-up for some cognitive measures, psychological intervention to improve mood may help to alleviate some difficulties.

The finding that people with epilepsy are cognitively compromised at baseline before the start of AED treatment means that many patients need to be re-educated about the potential causes of their cognitive impairment. Many patients with epilepsy attribute their cognitive problems to the side effects of their AED treatment (International Bureau for Epilepsy, 2004; Carpay *et al.*, 2005; Baker *et al.*, 2008), which may impact on treatment compliance. However, knowledge that they may have a learning and memory deficit (or another cognitive problem), which is part of their condition and not due to other factors, particularly their treatment, may relieve their anxiety about taking medication. Knowledge that cognitive impairments may be part of the clinical condition may also serve to reduce expectations of family and/or carers. Thompson (1997) suggests that confirmation of a memory deficit, in a young person who is struggling academically to achieve a standard comparable to their peers, may result in a reappraisal by the individual and their family and redirection to an alternative course that relies less on written examinations. However, lowered expectations may have a negative effect on self-esteem, effort and attitude about one's own abilities (Cornaggia *et al.*, 2006). Finally, education and specific epilepsy knowledge are important factors in the long-term self-care of epilepsy (Ridsdale, 2009); therefore, patients should be provided with information about the cognitive course of epilepsy so that they can learn how to manage its impact on their life.

9.7 Recommendations for future research

This thesis has highlighted several areas that may be worthy of future research. These will be discussed in the section below.

9.7.1 Investigation of the mechanisms underlying impairments

The finding of cognitive impairment at epilepsy onset in those without an underlying aetiology or known cerebral pathology implies a possible causal role for the underlying epileptogenesis or an unidentified neurobiological abnormality. The use of structural and functional imaging in conjunction with neuropsychological assessment may help to determine whether specific neuroabnormalities underlie these deficits.

Byars *et al.*, (2007) have explored the relationship between MRI structural abnormalities and neuropsychological functioning in children after a first recognised seizure. Similarly, Hermann *et al.*, (2006a) have correlated quantitative MRI volumetrics with cognitive functioning in children with idiopathic new-onset epilepsy. In addition, this group has found neuroanatomic abnormalities (e.g. abnormal cerebral volumes, cortical thinning and atrophy in subcortical structures) to be associated with poorer cognitive functioning in adults with TLE (Hermann *et al.*, 2007a; Dabbs *et al.*, 2009; Hermann *et al.*, 2009). Using diffusion tensor imaging, McDonald *et al.*, (2008) have also related white matter fibre tract integrity with language and memory performance in patients with TLE. Whilst these studies have increased our understanding of the abnormalities that might contribute to these cognitive deficits, there is a lack of similar studies in adults with new-onset epilepsy. Future work identifying the mechanisms that might lead to these cognitive impairments would be useful in predicting which patients have poorer neuropsychological functioning at diagnosis. Equally, longitudinal studies incorporating structural and functional imaging would be useful in revealing whether there are cerebral changes associated with increasing duration of epilepsy and whether these contribute to cognitive decline.

9.7.2 Development of prognostic models

As well as identifying mechanisms underlying cognitive impairments at baseline, there is a need to develop prognostic models in order to predict which patients are already at risk of cognitive impairments, and which are at risk of experiencing further cognitive decline, so that they can be referred for appropriate intervention and management.

9.7.3 Development of a core battery of neuropsychological measures

As discussed in Chapter 3 and Chapter 4, there is a lack of uniformity in the selection of neuropsychological tests in studies of people with epilepsy. This issue was highlighted by Cochrane *et al.* in 1998 but over a decade later, there is still no agreement on which cognitive measures should be used. A recent survey by Witt & Helmstaedter (2009) of 14 epilepsy centres in German-speaking countries identified over 200 tests, of which only a quarter were selected based on their evidence.

Despite repeated calls for uniformity and recommendations [e.g. the Neuropsychological Battery for Epilepsy (Dodrill, 1978), Baker & Marson (2001), EpiTrack (Lutz & Helmstaedter, 2005), NeuroCog Fx (Fliessbach *et al.*, 2006, Hoppe *et al.*, 2009)], these have not been consistently employed. In the longitudinal studies reviewed in Chapter 4, only four used the Neuropsychological Battery for Epilepsy (Dodrill & Wilensky 1990, 1992, Homes *et al.*, 1998, Dodrill, 2002). Unsurprisingly, these studies were those undertaken by the author of the battery. An interesting avenue for further research would be to qualitatively investigate the barriers to adoption of a core neuropsychological test battery. Understanding these barriers might help in the next stage of developing a core outcome set.

Developing standardised and agreed 'core outcome sets' for use in clinical trials and practice is gaining increasing support [e.g. Core Outcome Measures in Trials [(COMET) initiative]. Outcome sets have been identified for several other conditions, for example, rheumatoid arthritis, cystic fibrosis and bipolar affective disorder. They have the advantage of allowing easier comparison across trials and synthesis of results; reduce the risk of inappropriate outcomes being measured and reduce outcome reporting bias. In clinical practice it would be beneficial to have a universally agreed battery to act as a screening tool. This could be used to identify those who require more comprehensive neuropsychological evaluation or monitor changes in functioning as a result of AED treatment. Future work should concentrate on identifying a core battery of tests by utilising structured consensus techniques (e.g. semi-structured discussion at consensus meetings and Delphi techniques) to reach agreement among interested parties, such as clinicians, academic researchers and patient groups worldwide. This battery needs to assess the domains most affected in people with epilepsy;

be sensitive to change, as well as practical and cost-effective. This standardised approach has been adopted in the study of other neurological conditions, for example, multiple sclerosis (Rao, 1991, Benedict *et al.*, 2002) and has been advocated by other neuropsychologists working in the field of epilepsy (e.g. Baker *et al.*, 2009, Witt & Helmstaedter, 2009).

9.8 Conclusions

This research was conducted in the context of the SANAD trial. The SANAD trial was a prospective, randomised, pragmatic, unblinded, clinical trial, which provided a *unique* opportunity to investigate the natural history of cognitive functioning in people with newly diagnosed epilepsy. As a group, people with newly diagnosed epilepsy were cognitively compromised at the time of diagnosis. Once they started treatment, the majority had a different cognitive trajectory compared with healthy people from the general population. After an average of five years, they did not experience progressive declines on the majority of cognitive domains, although their performance on measures of memory and psychomotor speed were poorer compared with baseline. Memory and psychomotor speed measures were also the cognitive domains most affected at diagnosis and after 12 months.

However, not all people with epilepsy were affected. At baseline, 54% experienced cognitive dysfunction and 38% experienced cognitive decline after a mean five years. Therefore, all people with epilepsy should be screened for cognitive impairments at diagnosis, and monitored over time, so that those most at risk can be referred for more comprehensive neuropsychological assessment and appropriate intervention.

This research has contributed to our understanding of the cognitive course of cognitive functioning in people with new-onset epilepsy. This knowledge may help alleviate patient's anxiety about their own cognitive performance and inform them about likely changes over time. This research has attempted to identify the characteristics of those who had the most impairment and in doing so has highlighted other potential and important areas for further investigation.

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Appendix A SANAD Neuropsychology study

Dr. Gus A. Baker FBPsS

NEUROPSYCHOLOGICAL BATTERY FOR SANAD STUDY

1. Background Justification

Recent studies, that controlled for serum concentrations employing neuropsychological tests have reconfirmed cognitive side-effects of several antiepileptic drugs (AEDs) such as the central ('mental') slowing in patients using benzodiazepines or phenobarbital (Smith et a., 1987; Meador et al., 1987; Trimble & Thompson, 1984) and carbamazepine (Amman et al., 1990; Galassi et al., 1988). Accordingly, the prevention of adverse drug effects is given due attention both in the development of new AEDs and in clinical practice (Committee on Drugs, 1985; Gram, 1990; Aldenkamp 1990).

Most studies use neuropsychological testing procedures to assess these adverse effects. In clinical practice and in early (phase II, IIIa) drug trials (in which the largest patient groups are involved), the opportunities for such time-consuming assessments are usually very limited (Baker et al., 1991). Patient complaints, suggestive of problems in cognitive behaviour then often represent the only available evidence of possible cognitive dysfunction.

The SANAD study provides a unique opportunity to compare the neuropsychological profile of both established and novel AED's. A number of identified centres in the UK with previous experience of conducting clinical trials of AED's involving neuropsychological assessment will be invited to participate in this aspect of the SANAD trial.

2. Selection Of Battery

The following battery represents the recommendations of an International Cognitive Function Expert Panel which met in the USA in April 1996. The panel were commissioned to recommend a battery which would be most likely to detect a difference in neuropsychological functioning in a randomised clinical trial.

The panel first outlined the domains in which the battery should test and then went on to recommend the most appropriate test(s) in each of those domains. In making the recommendations the panel considered which tests had already been demonstrated to be sensitive to changes due to AEDs and might be the best to highlight benefits of new drugs over established drugs, based on what is currently known about the newer AED'S (see Table 1).

Table 1 Selection of tests and domains for the SANAD study

DOMAINS	TEST RECOMMENDED - AND COMMENTS
(i) Psychomotor Speed	Binary Choice Reaction Time - any would be acceptable but recommend the one form FePsy
(ii) Attention	Continuous Performance Task (computer version) - this should be put at the end of the battery for the best results
(iii) Memory	Pattern Recognition Test (from FePsy) Paragraphs (from Rivermead battery) Paired Associate Learning
(iv) Mental Flexibility	Colour & Colour-Word Tasks - both from Stroop
(v) Tracking Tasks	Any tracking task - recommend the one already performed with Lamicatal in volunteers (Cohen, et al.)
(vi) Mood	Profile of Mood Scale (POMS) Cornell Systymic Scale
(vii) Neurotoxicity	A-B Neurotoxicity Scale (patient-based)

The battery is easy to administer and is unlikely to take more than 40 minutes to complete. It should be administrated by a qualified Clinical Neuropsychologist but under exceptional circumstances other staff can be trained to conduct the tests as long as they are supervised by a clinical neuropsychologist. Centres agreeing to participate in the study will require minimal rsources as much of the battery can be administrated through the FEPSy a computerised software programme developed by Professor Bert Aldenkamp. There are a number of centres in the UK that already have experience in conducting this or similar batteries.

3. Timing

It is proposed that assessment of neuropsychological functioning should be conducted at the following three time points:

1. baseline
2. 3 months after enrolment
3. 12 months after enrolment

4. Costing

This will obviously depend on the number of subjects recruited to the study by each centre but it is envisaged that a 1/2 time assistant psychologist will be required for those centres able to recruit a substantial number of patients. The cost of providing a half-time assistant will be approximately £7500.

5. Power Calculations

A systematic review of randomised clinical trials of antiepileptic drug treatment employing a neuropsychological battery was recently conducted. A number of studies demonstrated significant cognitive effects when comparing different AED treatments. Little information is available from these studies in respect of sample size calculations. Obviously, neuropsychological tests were not always the primary outcome and therefore little consideration was given to such calculations. The following table provides some indication on the number of subjects used in previous trials and some of the differences observed.

Table 2. A selection of clinical trials using standard neuropsychological assessments

REFERENCE	COMPARISON AND DESIGN	NUMBER OF SUBJECTS	RESULTS PRESENTED
Smith et al, 1993	Lamotrigine v placebo – double blind cross over – add on study	62	No significant differences for limited battery
Kalvianen et al, 1995	VGB v CBZ – Newly diagnosed parallel study	100	Short term memory, Dot cancellation Task, colour naming task, category task etc. In favour of VGB
Meador et al, 1990	CBZ v PHT v pb – Double blind cross over	45	Digit symbol. In favour of CBZ and PHT
Mattson et al, 1985	CBZ v PB v PHT v PD – newly dignosed monotherapy parallel study	622	Finger tapping, colour naming, dst, and reaction time. In favour of CBZ

From the previously published data, it is estimated that the differences between two AED's, one with presumed side-effects (PHT) and one without (CBZ) on a psychomotor: the Finger-Tapping Test, requires larger sample sizes, as these differences are of smaller magnitude: 1/2 sd. (Mean 45.1 taps, s.d. 7.1). This would result in a required sample size of 15 patients for a crossover design and approximately 50 patients per arm in a parallel group design).

6. Centres To Be Involved

Centre	*Lead Psychologist*	*Lead Clinicians*
Manchester	Dr Hamira Riaz	Dr Paul Cooper
Liverpool	Dr Gus A. Baker	Prof David Chadwick /Dr Dave Smith
Birmingham	Mr Alan Moss	Dr Tim Betts / Dr Heaffield
Bristol	Mr Nigel Walton	Dr Jonathan Bird
Sheffield	Dr Paul Brooks	Dr Steve Howell
Glasgow	Dr Ruth Gillham	Dr Rod Duncan
London	Dr Robin Morris	Dr Robert Elwes / Dr Leena Nashef
Cambridge	Ms Rachel Blake	Dr Steve Rowe

Appendix B Neuropsychological tests

SANAD Number: _____ Subject Initials: _____ Centre No: _____ First Assessment

Rey Auditory Verbal Learning Test

Read the following passage to subjects before presenting word list:

"I am going to read a list of words. Please listen carefully – when I stop you are to say back as many words as you can remember. It doesn't matter in what order you repeat them. Just try to remember as many as you can."

Next present the word list to the left of the following table **at a rate of one word per second**. Following presentation look to subject, inviting their response. Record each correctly word with a tick.
When the subject indicates they can recall no more words read the following:

*"Now I'm going to read the same list again and once more when I stop I want you to tell me as many words as you can remember, **including words you said the first time**. Again, it doesn't matter in what order you say the words, just say as many as you can remember."*

Repeat these instructions prior to each of 5 repetitions of the test, recording responses in the following table.
Record the time at which the fifth trial is completed in the appropriate space below.
Following the fifth trial inform subjects that they will be asked to recall the words later during the session.
30 minutes following the fifth presentation read the following:

"Earlier I asked you to remember a list of words several times over. Could you tell me all the words from that list which you can remember."

Record those words recalled in the table below.

List A	1	2	3	4	5	Delay
DRUM						
CURTAIN						
BELL						
COFFEE						
SCHOOL						
PARENT						
MOON						
GARDEN						
HAT						
FARMER						
NOSE						
TURKEY						
COLOUR						
HOUSE						
RIVER						
Total						
					Sum=	Sum=

Time of 5th presentation	

USE BLACK BALL PEN - PRINT LEGIBLY

SANAD Number: _____ **Subject Initials:** _____ **Centre No:** _____ **First Assessment**

Paragraphs from RBMT-E

Read the following passage to subjects before reading the story:

"I am going to read you a passage of about five or six lines. Listen carefully and when I have finished tell me as much as you can remember. Ready?"

"Mr Brian / Kelly, / a Security Express employee / was shot dead / on Monday / during a bank raid / in Brighton. / The four raiders / all wore masks / and one carried / a sawn-off / shotgun. / Police detectives / were sifting through / eye-witness accounts last night. / A police spokesman said / "he was a very brave man. / He went for / the armed raider / and put up a hell of a fight."

"Now tell me as much of the story as you can."

Tick each story unit correctly recalled perfectly or using a close synonym. Each of these scores 1 point.

Circle each story unit partially recalled or recalled with an approximate synonym. Each of these scores ½ a point.

Time of completion of test	Initial recall score

Delayed Recall task

Ten minutes later read:

"Do you remember that story I read to you earlier? I would like to know how much of it you can remember now. Tell me as much as you can." Mark recall on paragraph below.

[If the subject cannot remember anything about the story then provide the following cue: *"It started off - Mr Brian Kelly, a security express employee…"* Note whether the subjected needed a cue.]

"Mr Brian / Kelly, / a Security Express employee / was shot dead / on Monday / during a bank raid / in Brighton. / The four raiders / all wore masks / and one carried / a sawn-off / shotgun. / Police detectives / were sifting through / eye-witness accounts last night. / A police spokesman said / "he was a very brave man. / He went for / the armed raider / and put up a hell of a fight."

Delayed recall score	Cue given?

USE BLACK BALL PEN - PRINT LEGIBLY

SANAD Number: _____ Subject Initials: _____ Centre No: _____ First Assessment

BENTON VERBAL FLUENCY TEST

	F	A	S
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

SUM F =	SUM A =	SUM S =
TOTAL =		

Years of education	Age 25-54		Age 55-59		Age 60-64	
	M	F	M	F	M	F
<9	9	8	11	10	14	12
9-11	6	5	7	7	9	9
12-15	4	3	5	4	7	6
15<	-	-	1	1	3	3

CORRECTION

ADJUSTED TOTAL

USE BLACK BALL PEN - PRINT LEGIBLY

Form C Stimulus Sheet

BLUE	RED	TAN	RED
GREEN	GREEN	RED	TAN
TAN	TAN	TAN	RED
RED	BLUE	BLUE	TAN
GREEN	GREEN	TAN	BLUE
BLUE	BLUE	RED	GREEN
GREEN	TAN	GREEN	RED
BLUE	GREEN	RED	BLUE
RED	TAN	BLUE	RED
BLUE	BLUE	TAN	TAN
TAN	GREEN	RED	GREEN
RED	BLUE	GREEN	TAN
TAN	GREEN	RED	BLUE
GREEN	RED	TAN	RED
BLUE	BLUE	BLUE	BLUE
TAN	GREEN	TAN	RED
GREEN	TAN	GREEN	GREEN
RED	RED	TAN	RED
TAN	TAN	BLUE	BLUE
RED	GREEN	TAN	TAN
TAN	TAN	BLUE	BLUE
RED	RED	GREEN	GREEN
GREEN	BLUE	RED	BLUE
RED	RED	GREEN	RED
TAN	GREEN	TAN	BLUE
BLUE	RED	RED	TAN
GREEN	TAN	GREEN	BLUE
TAN	BLUE	BLUE	GREEN

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Form C-W Stimulus Sheet

BLUE	GREEN	RED	GREEN
GREEN	BLUE	GREEN	TAN
RED	RED	BLUE	RED
TAN	BLUE	TAN	TAN
GREEN	TAN	RED	BLUE
BLUE	RED	TAN	TAN
RED	GREEN	BLUE	GREEN
TAN	TAN	TAN	RED
RED	GREEN	RED	GREEN
BLUE	BLUE	BLUE	RED
RED	RED	RED	BLUE
TAN	TAN	TAN	GREEN
BLUE	GREEN	BLUE	TAN
TAN	RED	GREEN	BLUE
RED	BLUE	TAN	GREEN
BLUE	GREEN	BLUE	RED
GREEN	RED	TAN	GREEN
TAN	GREEN	BLUE	TAN
GREEN	BLUE	RED	GREEN
TAN	TAN	GREEN	BLUE
RED	GREEN	BLUE	TAN
BLUE	RED	GREEN	BLUE
RED	TAN	BLUE	GREEN
TAN	BLUE	GREEN	RED
RED	TAN	RED	BLUE
TAN	RED	GREEN	GREEN
GREEN	TAN	TAN	RED
TAN	GREEN	RED	BLUE

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STROOP

Neuropsychological Screening Test

RECORD FORM

Max R. Trenerry, Ph.D.
Bruce Crosson, Ph.D.
James DeBoe, Ph.D.
William R. Leber, Ph.D.

Name _____

Sex _____ Age _____ Date _____

Reason for Referral _____

Diagnosis/Notes _____

_____

_____

SCORES

	Color Task	Color-Word Task
Number of Responses	_____	_____
Incorrect Responses	_____	_____
Score	_____	_____
Percentile		_____
Pr (Brain Damage)		_____

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Form C Responses – Color Task

1 BLUE_____	29 RED_____	57 TAN_____	85 RED_____
2 GREEN_____	30 GREEN_____	58 RED_____	86 TAN_____
3 TAN_____	31 TAN_____	59 TAN_____	87 RED_____
4 RED_____	32 BLUE_____	60 BLUE_____	88 TAN_____
5 GREEN_____	33 GREEN_____	61 TAN_____	89 BLUE_____
6 BLUE_____	34 BLUE_____	62 RED_____	90 GREEN_____
7 GREEN_____	35 TAN_____	63 GREEN_____	91 RED_____
8 BLUE_____	36 GREEN_____	64 RED_____	92 BLUE_____
9 RED_____	37 TAN_____	65 BLUE_____	93 RED_____
10 BLUE_____	38 BLUE_____	66 TAN_____	94 TAN_____
11 TAN_____	39 GREEN_____	67 RED_____	95 GREEN_____
12 RED_____	40 BLUE_____	68 GREEN_____	96 TAN_____
13 TAN_____	41 GREEN_____	69 RED_____	97 BLUE_____
14 GREEN_____	42 RED_____	70 TAN_____	98 RED_____
15 BLUE_____	43 BLUE_____	71 BLUE_____	99 BLUE_____
16 TAN_____	44 GREEN_____	72 TAN_____	100 RED_____
17 GREEN_____	45 TAN_____	73 GREEN_____	101 GREEN_____
18 RED_____	46 RED_____	74 TAN_____	102 RED_____
19 TAN_____	47 TAN_____	75 BLUE_____	103 BLUE_____
20 RED_____	48 GREEN_____	76 TAN_____	104 TAN_____
21 TAN_____	49 TAN_____	77 BLUE_____	105 BLUE_____
22 RED_____	50 RED_____	78 GREEN_____	106 GREEN_____
23 GREEN_____	51 BLUE_____	79 RED_____	107 BLUE_____
24 RED_____	52 RED_____	80 GREEN_____	108 RED_____
25 TAN_____	53 GREEN_____	81 TAN_____	109 BLUE_____
26 BLUE_____	54 RED_____	82 RED_____	110 TAN_____
27 GREEN_____	55 TAN_____	83 GREEN_____	111 BLUE_____
28 TAN_____	56 BLUE_____	84 BLUE_____	112 GREEN_____

Form C-W Responses – Color-Word Task

1 RED_____	29 BLUE_____	57 BLUE_____	85 TAN_____
2 BLUE_____	30 TAN_____	58 TAN_____	86 RED_____
3 GREEN_____	31 GREEN_____	59 RED_____	87 GREEN_____
4 BLUE_____	32 RED_____	60 GREEN_____	88 BLUE_____
5 RED_____	33 BLUE_____	61 TAN_____	89 TAN_____
6 TAN_____	34 GREEN_____	62 RED_____	90 GREEN_____
7 BLUE_____	35 BLUE_____	63 GREEN_____	91 RED_____
8 RED_____	36 GREEN_____	64 BLUE_____	92 TAN_____
9 TAN_____	37 RED_____	65 GREEN_____	93 BLUE_____
10 GREEN_____	38 TAN_____	66 TAN_____	94 GREEN_____
11 BLUE_____	39 BLUE_____	67 BLUE_____	95 RED_____
12 RED_____	40 RED_____	68 GREEN_____	96 TAN_____
13 TAN_____	41 BLUE_____	69 RED_____	97 RED_____
14 BLUE_____	42 TAN_____	70 BLUE_____	98 GREEN_____
15 GREEN_____	43 RED_____	71 RED_____	99 RED_____
16 RED_____	44 TAN_____	72 GREEN_____	100 BLUE_____
17 TAN_____	45 BLUE_____	73 BLUE_____	101 RED_____
18 GREEN_____	46 RED_____	74 TAN_____	102 BLUE_____
19 BLUE_____	47 GREEN_____	75 GREEN_____	103 TAN_____
20 RED_____	48 BLUE_____	76 BLUE_____	104 GREEN_____
21 TAN_____	49 TAN_____	77 RED_____	105 RED_____
22 GREEN_____	50 GREEN_____	78 TAN_____	106 TAN_____
23 BLUE_____	51 RED_____	79 GREEN_____	107 BLUE_____
24 GREEN_____	52 TAN_____	80 RED_____	108 TAN_____
25 TAN_____	53 GREEN_____	81 TAN_____	109 RED_____
26 BLUE_____	54 TAN_____	82 BLUE_____	110 BLUE_____
27 TAN_____	55 BLUE_____	83 GREEN_____	111 GREEN_____
28 RED_____	56 RED_____	84 BLUE_____	112 TAN_____

Percentile/Probability Table

Ages 18-49			Ages 50 –					
Raw Score	%ile	*Pr* Value	Raw Score	%ile	*Pr* Value	Raw Score	%ile	*Pr* Value
64		.98	<37		.99	85		.02
65		.97	37		.98	86		.01
66		.97	38		.98	87		.01
67		.97	39		.98	88	30	.01
68	2	.96	40		.97	89	32	.01
69		.96	41		.97	90		.01
70		.96	42		.96	91	36	.01
71		.95	43		.96	92		<.01
72		.95	44	2	.95	93	40	
73		.94	45		.94	94	42	
74		.93	46		.93	95		
75		.93	47		.92	96	44	
76		.92	48		.90	97	50	
77	3	.91	49		.89	98		
78	4	.90	50		.87	99	52	
79		.89	51		.85	100		
80		.88	52		.83	101	56	
81		.87	53		.80	102	60	
82	5	.86	54		.77	103	64	
83		.84	55		.74	104		
84		.83	56		.71	105		
85	6	.81	57	4	.67	106	66	
86	8	.80	58	8	.63	107	68	
87		.78	59	10	.59	108	70	
88		.76	60		.55	109	72	
89		.74	61		.51	110	76	
90	9	.72				111	78	
91		.70	62		.47	112	100	
92	12	.68	63		.43			
93	15	.65	64	12	.38			
94		.63	65	14	.34			
95	17	.60	66		.31			
96	18	.58	67		.27			
97	19	.55	68		.24			
98	20	.52	69		.21			
			70		.18			
99	21	.50	71		.16			
100	25	.47	72	16	.14			
101	26	.44	73		.12			
102	29	.42	74	20	.10			
103	32	.39	75		.09			
104	34	.37	76		.08			
105	35	.34	77		.06			
106	36	.32	78		.05			
107	39	.30	79		.05			
108	42	.27	80		.04			
109	44	.25	81		.03			
110	51	.23	82		.03			
111	69	.22	83		.02			
112	100	.20	84	24	.02			

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AMIPB

INFORMATION PROCESSING A

FORM 1

NAME _____ DATE _____

AGE _____ DOB _____ REF. NO. _____

Demonstration

38, 25, 79

97, 22, 18, 65

85, 27, 20, 48, 52

72, 50, 23, 74, 16

92, 18, 54, 77, 21

46, 39, 38, 16, 72

17, 54, 83, 11, 80

26, 87, 66, 39, 48

54, 56, 51, 63, 22

Demonstration

11

11

11

11

11

	Score	%ile range
Task A Total	_____	_____
Errors %	_____	_____
Speed	_____	_____
Adjusted	_____	_____

Motor Speed

11	11	11
11	11	11
11	11	11

91, 26, 43, 82, 17
61, 59, 62, 18, 80
27, 48, 92, 36, 28
53, 29, 61, 19, 32
32, 41, 18, 24, 11

24, 82, 58, 26, 41
80, 36, 72, 43, 65
74, 19, 41, 28, 50
55, 41, 60, 11, 13
60, 99, 20, 22, 48

51, 29, 81, 16, 99
18, 32, 67, 77, 33
42, 83, 17, 56, 40
36, 98, 39, 19, 14
80, 22, 82, 75, 57

65, 26, 11, 72, 22
37, 55, 18, 53, 90
92, 49, 27, 19, 83
94, 93, 64, 11, 65
14, 18, 83, 73, 10

90, 52, 81, 23, 39
12, 49, 59, 92, 87
55, 27, 36, 84, 66
55, 86, 29, 38, 22
33, 55, 41, 61, 65

37, 51, 19, 36, 84
27, 64, 48, 63, 20
18, 16, 71, 23, 62
28, 21, 92, 74, 61
26, 54, 51, 29, 60

43, 52, 41, 80, 10
85, 22, 16, 45, 53
57, 17, 68, 98, 80
17, 23, 15, 30, 36
20, 53, 50, 72, 29

28, 62, 19, 12, 54
42, 25, 41, 33, 38
17, 12, 18, 15, 29
86, 42, 93, 28, 71
76, 72, 40, 60, 29

63, 20, 82, 18, 99
28, 40, 23, 76, 77
12, 15, 38, 65, 71
17, 57, 41, 91, 28
32, 39, 14, 56, 42

52, 91, 17, 86, 68
21, 20, 50, 94, 54
70, 13, 38, 62, 69
43, 21, 16, 50, 56
45, 48, 89, 21, 12

82, 37, 21, 97, 79
66, 29, 59, 23, 32
71, 62, 50, 82, 44
64, 97, 91, 63, 95
56, 12, 82, 43, 20

93, 78, 50, 12, 15
32, 70, 92, 65, 80
18, 29, 54, 28, 30
25, 56, 41, 39, 20
94, 34, 29, 36, 14

72, 26, 34, 61, 79
68, 17, 72, 65, 81
61, 98, 60, 27, 41
12, 83, 70, 65, 32
45, 72, 24, 59, 10

14, 45, 89, 53, 21
35, 58, 41, 65, 28
63, 30, 93, 21, 45
94, 92, 16, 82, 24
22, 59, 21, 75, 48

26, 56, 28, 93, 40
54, 90, 26, 81, 15
32, 37, 91, 15, 22
11, 42, 86, 90, 19
19, 53, 18, 92, 64

28, 21, 81, 47, 68
57, 52, 10, 69, 92
41, 60, 56, 78, 69
94, 79, 38, 20, 29
26, 94, 37, 50, 29

90, 27, 83, 41, 86
87, 15, 10, 85, 90
22, 56, 74, 36, 57
73, 80, 12, 72, 84
95, 41, 81, 70, 18

41, 30, 94, 50, 58
24, 95, 75, 81, 72
59, 26, 57, 19, 36
52, 17, 23, 60, 28
52, 68, 62, 30, 74

27, 29, 16, 23, 38
83, 81, 75, 77, 89
91, 61, 54, 80, 59
79, 82, 47, 16, 52
80, 83, 29, 90, 10

61, 14, 15, 50, 47
44, 19, 65, 24, 13
42, 40, 55, 84, 73
37, 49, 45, 38, 27
55, 25, 86, 20, 46

61, 96, 82, 85, 74
27, 86, 50, 16, 11
43, 30, 99, 36, 22
48, 50, 60, 44, 82
68, 27, 63, 37, 45

AMIPB

INFORMATION PROCESSING B

FORM 1

NAME _____ DATE _____

AGE _____ DOB _____ REF. NO. _____

Demonstration

3 1 - 1 3 9

2 7 5 - 5 8 7 2

5 2 1 6 - 6 1 4 2 5

3 7 9 9 - 5 9 7 3 9

2 6 9 5 - 1 2 5 6 9

1 4 4 8 - 8 4 0 4 1

5 0 2 7 - 2 0 7 3 5

6 9 8 1 - 4 8 1 6 9

7 2 1 6 - 2 6 1 7 8

Demonstration

11

11

11

11

11

	Score	%ile range
Task B Total	_____	_____
Errors %	_____	_____
Speed	_____	_____
Adjusted	_____	_____

Motor Speed

11	11	11
11	11	11
11	11	11

5184 - 13485
2910 - 71092
8024 - 24089
7514 - 76145
5672 - 27356

2941 - 17429
2824 - 82124
1309 - 93081
9467 - 57496
5436 - 73546

1768 - 67841
4923 - 63942
4594 - 44597
2156 - 51326
3182 - 27831

4691 - 96415
3832 - 38213
2527 - 57282
1496 - 16549
9134 - 45193

6012 - 20861
9063 - 62390
6572 - 75261
8489 - 88049
3817 - 21783

3556 - 52563
8719 - 97148
2478 - 74286
4539 - 95346
7952 - 82795

3864 - 46893
6379 - 93867
4920 - 30429
4713 - 13745
9474 - 49417

5238 - 84325
6022 - 20962
4953 - 84953
6597 - 75689
4818 - 18845

4157 - 57140
2581 - 86251
8043 - 40893
2218 - 21248
2709 - 74290

6316 - 56631
5748 - 38475
1246 - 12964
4926 - 26941
3295 - 59362

4005 - 50240
3967 - 72396
1081 - 98011
9261 - 21968
4513 - 37514

2716 - 91672
8407 - 83047
9165 - 65192
4756 - 84765
9039 - 36909

4683 - 38624
3157 - 47135
7256 - 65270
1964 - 14695
4875 - 45978

6719 - 92716
9421 - 12394
1082 - 80162
9354 - 54319
1759 - 13795

5619 - 91625
8723 - 30872
6556 - 64565
1912 - 29113
7024 - 70842

9127 - 21794
8352 - 53298
1034 - 30541
5243 - 64253
8979 - 68979

6317 - 71643
5418 - 25481
9037 - 70329
4521 - 15642
6459 - 84695

3078 - 87430
2972 - 72219
6180 - 67081
1245 - 15342
4126 - 21647

5982 - 90852
4176 - 67413
1289 - 92815
6134 - 41763
3519 - 61935

1028 - 85021
4695 - 74659
7138 - 83417
5029 - 92560
5814 - 49851

7069 - 90762
3518 - 51843
4276 - 36724
7129 - 20917
4518 - 84152

NAME _____ DATE _____

SEX: Male (M) Female (F)

IDENTIFICATION

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

The numbers refer to these phrases.

0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

Col (C) O.P. (O)

	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1. Friendly	0	1	2	3	4
2. Tense	0	1	2	3	4
3. Angry	0	1	2	3	4
4. Worn out	0	1	2	3	4
5. Unhappy	0	1	2	3	4
6. Clear-headed	0	1	2	3	4
7. Lively	0	1	2	3	4
8. Confused	0	1	2	3	4
9. Sorry for things done	0	1	2	3	4
10. Shaky	0	1	2	3	4
11. Listless	0	1	2	3	4
12. Peeved	0	1	2	3	4
13. Considerate	0	1	2	3	4
14. Sad	0	1	2	3	4
15. Active	0	1	2	3	4
16. On edge	0	1	2	3	4
17. Grouchy	0	1	2	3	4
18. Blue	0	1	2	3	4
19. Energetic	0	1	2	3	4
20. Panicky	0	1	2	3	4
21. Hopeless	0	1	2	3	4
22. Relaxed	0	1	2	3	4
23. Unworthy	0	1	2	3	4
24. Spiteful	0	1	2	3	4
25. Sympathetic	0	1	2	3	4
26. Uneasy	0	1	2	3	4
27. Restless	0	1	2	3	4
28. Unable to concentrate	0	1	2	3	4
29. Fatigued	0	1	2	3	4
30. Helpful	0	1	2	3	4
31. Annoyed	0	1	2	3	4
32. Discouraged	0	1	2	3	4
33. Resentful	0	1	2	3	4
34. Nervous	0	1	2	3	4
35. Lonely	0	1	2	3	4
36. Miserable	0	1	2	3	4
37. Muddled	0	1	2	3	4
38. Cheerful	0	1	2	3	4
39. Bitter	0	1	2	3	4
40. Exhausted	0	1	2	3	4
41. Anxious	0	1	2	3	4
42. Ready to fight	0	1	2	3	4
43. Good natured	0	1	2	3	4
44. Gloomy	0	1	2	3	4
45. Desperate	0	1	2	3	4
46. Sluggish	0	1	2	3	4
47. Rebellious	0	1	2	3	4
48. Helpless	0	1	2	3	4
49. Weary	0	1	2	3	4
50. Bewildered	0	1	2	3	4
51. Alert	0	1	2	3	4
52. Deceived	0	1	2	3	4
53. Furious	0	1	2	3	4
54. Efficient	0	1	2	3	4
55. Trusting	0	1	2	3	4
56. Full of pep	0	1	2	3	4
57. Bad-tempered	0	1	2	3	4
58. Worthless	0	1	2	3	4
59. Forgetful	0	1	2	3	4
60. Carefree	0	1	2	3	4
61. Terrified	0	1	2	3	4
62. Guilty	0	1	2	3	4
63. Vigorous	0	1	2	3	4
64. Uncertain about things	0	1	2	3	4
65. Bushed	0	1	2	3	4

MAKE SURE YOU HAVE ANSWERED EVERY ITEM.

EdITS POM 021

SANAD Number: _____ Subject Initials: _____ Centre No: _____ First Assessment

THE A-B NEUROPSYCHOLOGICAL ASSESSMENT SCHEDULE

PLEASE THINK ABOUT EACH OF THE FOLLOWING STATEMENTS - TO WHAT EXTENT DO YOU AGREE WITH EACH?

IF IT IS NOT A PROBLEM YOU HAVE RING 0 IF IT IS A MILD PROBLEM RING 1
IF IT IS A MODERATE PROBLEM RING 2 IF IT IS A SERIOUS PROBLEM RING 3.

IF A QUESTION IS NOT RELEVANT TO YOU, NO ANSWER SHOULD BE GIVEN.

	No Problem ↓	A mild problem ↓	A moderate problem ↓	A serious problem ↓
1. I am less enthusiastic about day to day activities	0	1	2	3
2. My mind does not work as fast as it should	0	1	2	3
3. I have difficulties remembering people's names	0	1	2	3
4. I have difficulties in following books or films	0	1	2	3
5. I feel clumsy	0	1	2	3
6. I have problems finding the correct words	0	1	2	3
7. I am less capable of undertaking initiatives	0	1	2	3
8. My thinking has slowed down	0	1	2	3
9. I forget all kind of things, for example an appointment or where I put an object	0	1	2	3
10. I have difficulties concentrating on the things I am doing	0	1	2	3
11. I cannot use a pen or pencil accurately	0	1	2	3
12. I have problems understanding what I read	0	1	2	3
13. I tire easily and have little energy	0	1	2	3
14. It takes me longer to do things these days	0	1	2	3

	No Problem	A mild problem	A moderate problem	A seriou problem
	↓	↓	↓	↓
15. I forget things that people have said to me	0	1	2	3
16. I can't concentrate for more than a short period of time	0	1	2	3
17. I constantly bump against tables, doorframes etc.	0	1	2	3
18. I feel worn out	0	1	2	3
19. It takes more time for me to start doing things	0	1	2	3
20. I get confused and forget what I was doing	0	1	2	3
21. I get distracted more easily	0	1	2	3
22. I sometimes stutter or am unable to find the correct words	0	1	2	3
23. I feel I react too slowly to things that are said to me	0	1	2	3
24. I cannot keep an activity going for long	0	1	2	3

ARE YOU AWARE OF ANY OTHER PROBLEMS NOT MENTIONED IN THE QUESTIONS? PLEASE WRITE THEM DOWN AND RING 0, 1 ,2 OR 3:

	↓	↓	↓	↓
1.	0	1	2	3
2.	0	1	2	3
3.	0	1	2	3
4.	0	1	2	3
5.	0	1	2	3
6.	0	1	2	3
7.	0	1	2	3
8.	0	1	2	3
9.	0	1	2	3
10.	0	1	2	3

ABNAS Score

USE BLACK BALL PEN - PRINT LEGIBLY

Appendix C Supplementary data

Table C.1: Regression equations used to create age, sex and education adjusted z-scores

Variable	Constant	Predictors	SE estimate
Finger Tapping Task			
Dominant hand	61.487		6.65594
Non-dominant hand	53.851		5.89813
Log Visual RT			
Dominant hand	5.673	(0.003**age*)- (0.066**sex*)	0.12804
Non-dominant hand	5.759	(-0.079**sex*)	0.14561
Log CVST	2.118	(0.007**age*)	0.26818
Word recognition task			
Serial	15.758		3.66713
Figure recognition task			
Serial	17.491		4.07817
Story recall			
Immediate	10.148	(1.840**educ_d1*)+(1.778**educ_d2*)-(0.064**age*)	3.04695
Delayed	9.276	(1.91**educ_d1*)-(0.060**age*)	3.12982
Rey AVLT			
Immediate recall	57.476	(-0.147**age*)	9.40136
Delayed recall	13.431	(-1.484**sex*)-(0.042**age*)-(1.898**educ_d1*)	3.06952
Benton verbal fluency	33.975	(6.253**educ_d1*)+(7.054**educ_d2*)	10.53
AMIPB			
Info Processing	67.284	(10.620**educ_d1*)+(10.403**educ_d2*)-(0.273**age*)	14.72407
Psychomotor speed	56.339	(5.502**educ_d2*)-(0.199**age*)	6.45750

Table C.2: Regression equations used to create standardised regression-based change scores

Variable	R2	Constant	Baseline	Predictors	SE estimate
Finger Tapping					
Dominant hand	.607	13.135	0.797		4.6217
Non-dominant hand	.734	7.325	0.920		3.41862
Log Visual RT					
Dominant hand	.321	5.262	0.001		0.11292
Non-dominant hand	.373	5.317	0.001		0.09237
BCRT	.606	169.345	0.348	+(1.887*age at baseline)	41.46380
Log CVST	.524	1.722	0.050	+(0.005*age at baseline) -(0.145*educ_d2)	0.21383
Word recog					
Serial	.425	.6509	0.632		3.41451
Figure recog					
Serial	.378	10.859	0.444	+(1.787*sex)	3.29808
Story recall					
Immediate	.580	1.838	0.810		2.49282
Delayed	.606	2.749	0.863		2.53305
Rey AVLT					
Immediate recall	.577	25.916	0.611	(-0.129*age at baseline)	6.38064
Delayed recall	.611	5.822	0.593	(-0.042*age at baseline)	1.85842
Verbal fluency	.667	10.643	0.776		5.93785
AMIPB					
Info Processing	.880	6.369	0.952		5.70015
Psychomotor speed	.719	6.900	0.907		4.78113

Appendix D Related publications

Epilepsia, 51(1):48–56, 2010
doi: 10.1111/j.1528-1167.2009.02195.x

FULL-LENGTH ORIGINAL RESEARCH

Patients with epilepsy: Cognitively compromised before the start of antiepileptic drug treatment?

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***Division of Neurological Science, †Centre for Medical Statistics and Health Evaluation, University of Liverpool, Liverpool, United Kingdom; ‡The Welsh Epilepsy Unit, University Hospital of Wales, Cardiff, United Kingdom; and §Epilepsy Centre Kempenhaeghe and Department of Neurology, Maastricht University Hospital, Maastricht, The Netherlands**

Summary

Purpose: To compare the cognitive profile of newly diagnosed untreated epilepsy patients with healthy volunteers using a comprehensive neuropsychological test battery.

Methods: A total of 155 untreated patients with newly diagnosed epilepsy, and no known brain pathology, were assessed before the start of treatment with antiepileptic medication. Their scores across the neuropsychological measures were compared with 87 healthy volunteers from the general population equated for age and sex.

Results: After adjusting for age, sex, and education, patients with epilepsy performed significantly worse than healthy volunteers on 6 of 14 cognitive measures, particularly in the domains of memory and psychomotor speed. Cognitive performance was not related to the number of seizures, type of epilepsy, or mood. When an impairment index was calculated, 53.5% patients had a least one abnormal score [>2 standard deviations (SD) below the control mean] on the test battery compared with 20.7% of healthy volunteers.

Discussion: Newly diagnosed untreated patients with epilepsy are cognitively compromised before the start of antiepileptic drug medication. The domains most affected are memory and psychomotor speed. More than one-half of the patients had at least one abnormal test score across the test battery. There were no differences in epilepsy-related or mood variables between those who demonstrated dysfunction and those that did not.

KEY WORDS: Epilepsy, Newly diagnosed epilepsy, Neuropsychology, Cognitive functioning, Cognition.

Many people with epilepsy report impairments in their cognitive functioning. The main factors that appear to contribute to cognitive dysfunction in people with epilepsy are the side effects of antiepileptic medication, the underlying etiology of their epilepsy, psychosocial issues, and the effects of recurrent seizures (Kwan & Brodie, 2001; Meador, 2002; Aldenkamp & Bodde, 2005). There is some evidence to suggest that these reported impairments deteriorate over time (Dodrill, 2004; Seidenberg et al., 2007), although there is contrary evidence to suggest that these impairments remain stable and do not represent a progressive dementia-like disorder (Holmes et al., 1998; Helmstaedter & Elger, 1999).

A number of studies have suggested that these impairments are already present in people with epilepsy, before the start of their antiepileptic treatment and following few seizures; hence at epilepsy onset (Smith et al., 1987; Kälviäinen et al., 1992; Äikiä et al., 1995; Prevey et al., 1998; Äikiä et al., 2001; Pulliainen et al., 2000a). This implies that at least part of the cognitive impairment is not caused by the accumulating effects of seizures and medication but may be the result of epileptogenesis. These impairments occur across several cognitive domains, with previously untreated patients with newly diagnosed epilepsy performing worse than healthy volunteers on

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measures of attention, concentration, motor function, mental flexibility, memory, and learning. However, one study reported that although patients performed worse than healthy volunteers on measures of attention, learning, delayed recall, and recognition, it was a proportion (30%) of patients with epilepsy that demonstrated subtle memory and attention dysfunction (Kälviäinen et al., 1992).

We have investigated further the cognitive profile of newly diagnosed untreated patients with epilepsy compared with healthy volunteers from the general population, using a comprehensive neuropsychological test battery. This study forms part of a longitudinal study investigating the natural history of cognitive impairment in patients with newly diagnosed epilepsy.

Methods

Design

This study was conducted as part of the larger Standard and New Antiepileptic Drugs (SANAD) trial (Marson et al., 2007a,b); a prospective multicenter unblinded randomized clinical trial assessing the clinical and cost-effectiveness of standard and new antiepileptic drugs (AEDs). The focus of this article is on comparison of the baseline assessment between patients with epilepsy and healthy volunteers, in order to increase our understanding of the cognitive deficits experienced by patients with newly diagnosed epilepsy prior to starting AED treatment.

Participants

Patients with epilepsy

The SANAD study recruited patients with epilepsy from hospital outpatient clinics at 90 hospital centers in the United Kingdom. Patients were recruited into SANAD between October 2000 and August 2004. Patients were recruited if they satisfied the inclusion criteria consisting of a history of two or more clinically definite unprovoked epileptic seizures in the previous year and if treatment with a single AED represented the best therapeutic option. This allowed inclusion of patients with newly diagnosed epilepsy; patients who had failed treatment with previous monotherapy (provided that the drug failure did not include one of the drugs present in the randomization) and patients in remission of epilepsy, who had relapsed following the withdrawal of treatment. Patients were excluded if the clinician or patient felt that treatment was contraindicated, if all their seizures had been acute symptomatic seizures, or if there was a history of progressive neurologic disease.

At the time of randomization into SANAD, those patients who were newly diagnosed, previously untreated, and older than 15 years of age, from 10 of the hospital centers, were invited to participate in the neuropsychology part of the study. They were assessed before the administration of antiepileptic medication (min 0-max 13 days after randomization) and were reassessed after 3 and 12 months of treatment with randomized study drug.

A total of 257 patients with newly diagnosed epilepsy were initially recruited and assessed. Three patients were excluded because they were subsequently found not to have epilepsy, and a further 31 were excluded because they had been treated previously with AEDs. Thirty-nine patients had either learning disability or previous or current neurologic disorder, for example, stroke, intracranial surgery, head injury, and meningitis, which can impair cognitive functioning, and so these patients were also excluded from the analysis. An additional 29 were found to have abnormal neuroimaging on clinical magnetic resonance imaging (MRI). Because we wanted to investigate the impact of seizures and epilepsy and not the impact of a specific structural lesion, these patients were also excluded from this analysis. Therefore, this analysis focuses on 155 untreated patients with newly diagnosed epilepsy who were otherwise neurologically normal.

Healthy volunteers

Eighty-seven healthy volunteers were recruited from the general population to act as a control group. Healthy volunteers from the general population have been used as a comparison group in several similar studies (Smith et al., 1987; Kälviäinen et al., 1992; Äikiä et al., 1995; Prevey et al., 1998; Pulliainen et al., 2000a; Äikiä et al., 2001). The use of a healthy volunteer group allows us to evaluate whether patients with epilepsy already differ from their peers in terms of cognitive functioning at the time of diagnosis. The healthy volunteers were recruited between March 2007 and October 2007. Efforts were made to equate the healthy volunteer group to the epilepsy group in age and sex. Healthy volunteers were not considered eligible for the study if they had a history of neurologic or psychiatric disorders, had a previous head injury, had previously been treated with AEDs, or had a history of substance abuse. Neurologic and psychiatric history was assessed informally by self-report in a semistructured interview prior to assessment.

The number of healthy volunteers recruited into the study was based on the finger tapping task. The tapping task was used in the sample size calculation, as it is thought to be sensitive to the effects of AED treatment and is one of the most frequently used tests employed in randomized clinical trials (Cochrane et al., 1998). To have a power of at least 80% to detect a difference between the two groups (patient and control), of approximately one-third standard deviations (SDs), 87 healthy volunteers were needed.

Neuropsychological test battery

The neuropsychological test battery was selected to be most able to detect a difference between drugs in a

Table 1. Neuropsychological test battery

Domain	Test (references)	Outcome variable
Psychomotor speed	Finger tapping (Alpherts, 1987)	The average number of taps for the dominant and nondominant hands across five trials
	Visual reaction time (Alpherts, 1987)	The average reaction time for the dominant and nondominant hands (ms)
	AMIPB psychomotor speed (Coughlan & Hallows, 1985)	The mean number of digits crossed through over two trials
Memory	Recognition of words/figures (Alpherts, 1987)	The number of words or figures correctly answered on the serial/simultaneous version of the task
	Rey Auditory Verbal Learning Task (Rey, 1964)	The sum of the words recalled over the five trials and the number of words recalled after a 30-min delay
	Story recall (Wilson et al., 1989)	The immediate and delayed recall score
Information processing	AMIPB information processing (Coughlan & Hallows, 1985)	The mean number of correct responses over the two tasks
	Binary choice reaction time (Alpherts, 1987)	The average response speed (ms)
	Computerized Visual Search Task (Alpherts, 1987)	The average speed of response (s)
Mental flexibility	Stroop (Trenerry et al., 1989)	The number of correct responses on the color-word task
	Benton verbal fluency (Benton & Hamsher, 1976)	The total number of acceptable words produced
Mood	Profile of Mood State (McNair et al., 1992)	Transformed scores (/100) for each mood factor

AMIPB, Adult Memory and Information Processing Battery.

randomized clinical trial (Baker & Marson, 2001). The battery, illustrated in Table 1, comprised measures from the *FePsy Computerized Test Battery* (Alpherts, 1987) and traditional paper-and-pencil measures. The FePsy was administered, as it is thought to be sensitive to detect subtle cognitive effects of AEDs and has been developed specifically for use with people with epilepsy (Baker et al., 1998).

The neuropsychological test battery took approximately one and a half hours to complete. Tests were administered in a set order to ensure adequate time passed to test delayed recall on the memory subtests. However, regular breaks were offered and taken to reduce fatigue effects. Neuropsychological assessment was postponed and rearranged for a later date in those patients who reported having a seizure within 24 h of the assessment. The study was approved by the North West Research Ethics Committee. All participants in the study provided written informed consent.

Statistical analysis

Data were analyzed using SPSS version 16.0 (SPSS Inc, Chicago, IL, U.S.A.). Independent *t*-tests and chi-square tests were carried out to investigate any differences in demographics between patients with epilepsy and healthy volunteers.

Independent *t*-tests, Mann-Whitney *U* test, and chi-square test were performed on the neuropsychological test variables to detect statistically significant differences between the two groups. Ceiling effects were observed on the Stroop Neuropsychological Screening Test, so this variable was converted to a categorical one based on normative data (Trenerry et al., 1989). Five variables were skewed so three of these were log-transformed so they met the assumption of normality for parametric analysis. Scores on the binary choice reaction time and simultaneous recognition of words became more skewed after transformations so nonparametric analyses were carried out on these.

Raw scores on the 14 normally distributed neuropsychological test variables were converted to *z*-scores adjusted for age, sex, and education relative to the control mean (mean = 0, SD = 1) using multiple regression techniques. This method has been employed in previous studies involving adults and children with epilepsy (Oyegbile et al., 2004; Hermann et al., 2006, 2007). This method was used because it corrects for the effects of age, sex, and education, which are important potentially confounding variables on cognitive functioning. In addition, by putting all scores on a common metric, comparisons across tests and across domains can be made directly (Oyegbile et al., 2004; Hermann et al., 2006, 2007).The adjusted *z*-scores were transformed by multiplying the timed tasks by −1, so that higher scores on all tasks reflect better performance.

Spearman's rho correlations were carried out to investigate the relationship between neuropsychological test performance, mood, and previous seizure activity. One-way between-subjects analyses of variance (ANOVAs) were conducted to investigate differences in epilepsy type.

To investigate the clinical significance of results, a summary impairment index was created, which represents the proportion of test scores that are classified as abnormal. This reflects the degree of cognitive impairment exhibited by each individual (Oyegbile et al., 2004; Hermann et al., 2006, 2007). Exploratory analyses were conducted to investigate the demographic and clinical characteristics of those with cognitive impairment.

The significance level was set at $p < 0.01$. This was to reduce the likelihood of making a type I error due to the number of multiple comparisons being made. A Bonferroni correction could have been applied; however, given the number of inferential tests and exploratory analyses conducted this would have been too conservative a value and would have increased the likelihood of making a type II error.

Results

Baseline clinical and demographic characteristics

Supplementary Table S1 illustrates the demographic and clinical characteristics of patients with epilepsy and healthy volunteers at baseline. There were no differences in age ($p = 0.962$) and sex ($p = 0.910$) between the groups. The healthy volunteers had significantly more years of education than the patients with epilepsy ($p < 0.001$).

Differences between patients with epilepsy and healthy volunteers

Table 2 compares the performance of patients with epilepsy and healthy volunteers across the neuropsychological test battery at baseline. Looking at the raw scores, patients performed worse than healthy volunteers on 13 of 16 cognitive measures, and this reached statistical significance for 10 of 16 measures. On the Stroop Neuropsychological Screening Test, after adjusting for age, significantly more patients with epilepsy (31.5%) than healthy volunteers (4.8%) fell in the borderline ranges. Significantly fewer patients with epilepsy (55.0%) compared with healthy volunteers (84.5%) fell in the average ranges ($\chi^2 = 25.03$, d.f. = 2, $p < 0.001$).

Fig. 1 plots the patients' performance across the neuropsychological test battery with the *x*-axis representing the

Table 2. Baseline performance of patients with epilepsy compared with healthy volunteers

Variable	Patients with epilepsy (mean, SD, n)	Controls (mean, SD, n)	Diff (95% CI)	p-value
Finger tapping				
Dominant	57.11 (9.25, 144)	61.10 (6.61, 81)	−3.99 (−6.09, −1.89)	<0.001*
Nondominant	52.03 (7.87, 144)	55.02 (5.86, 81)	−2.99 (−4.97, −1.02)	0.003*
Log visual RT (ms)[a]				
Dominant	5.71 (0.22, 143)	5.72 (0.14, 87)	−0.01 (−0.06, 0.3)	0.563
Nondominant	5.69 (0.18, 144)	5.74 (0.15, 87)	−0.05 (−0.10, −0.01)	0.022
Log CVST (s)[a]	2.34 (0.29, 151)	2.27 (0.29, 86)	0.07 (−0.01, 0.15)	0.082
Word recognition				
Serial	15.39 (4.11, 152)	16.10 (3.76, 87)	−0.71 (−1.76, 0.35)	0.187
Figure recognition				
Serial	14.42 (3.85, 149)	16.73 (4.08, 87)	−2.31 (−3.36, −1.27)	<0.001*
Story recall				
Immediate	7.69 (2.92, 155)	9.92 (3.26, 87)	−2.23 (−3.04, −1.43)	<0.001*
Delayed	6.78 (3.06, 155)	9.02 (3.31, 87)	−2.24 (−3.07, −1.41)	<0.001*
Rey AVLT				
Immediate	45.17 (9.66, 155)	50.70 (9.66, 87)	−5.53 (−8.08, −2.98)	<0.001*
Delayed	8.80 (3.33, 155)	10.37 (3.28, 87)	−1.57 (−2.44, −0.69)	<0.001*
Verbal fluency	34.15 (11.58, 155)	41.75 (10.70, 87)	−7.59 (−10.57, −4.62)	<0.001*
AMIPB				
Info processing	60.15 (15.89, 155)	68.17 (15.69, 87)	−8.02 (−12.19, −3.84)	<0.001*
Psychomotor speed	46.44 (9.85, 152)	51.86 (7.47, 87)	−5.42 (−7.65, −3.19)	<0.001*
Binary choice RT (ms)[a,b]	354.00 (306.00–426.00, 147)	359 (318.75–410.00, 86)	0.00 (−19.00, 20.00)	0.986
Word recognition[b]				
Simultaneous	20.00 (18.00–22.00, 152)	21.00 (18.00–22.00, 84)	−1.00 (−1.00, 0.00)	0.157

Data was missing for various reasons, for example, participants refused to complete the task, computer error meant FePsy data was not recorded.

RT, reaction time; CVST, Computerized Visual Search Task; Rey AVLT, Rey Auditory Verbal Learning Test; AMIPB, Adult Memory and Information Processing Battery.

[a]Lower scores reflect better performance.

[b]Values reported are median, 25th–75th percentiles.

*Significant at $p < 0.01$.

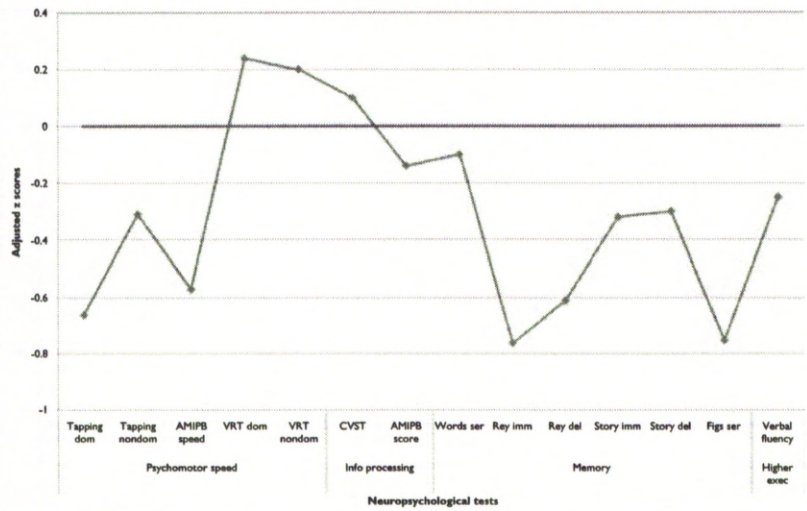

Figure 1.
Performance of patients with epilepsy across the neuropsychological test battery relative to healthy volunteers (straight line). The *x*-axis represents the mean performance of the healthy volunteers. Dom, dominant; nondom, nondominant; AMIPB, Adult Memory and Information Processing Battery; VRT, visual reaction time; CVST, Computerized Visual Search Task; ser, serial; imm, immediate; del, delayed.
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control mean. After adjusting for sex, age, and education, there were statistically significant differences on 6 of 14 measures. Patients demonstrated significantly worse performance on the finger tapping task with the dominant hand ($p < 0.001$). They performed more poorly on the motor speed task of the Adult Memory and Information Processing Battery ($p < 0.001$). They recognized fewer figures on the serial recognition task ($p < 0.001$). They recalled fewer words immediately ($p < 0.001$) and after a delay ($p < 0.001$) on the Rey Auditory Verbal Learning Task. They also recalled significantly fewer units of a story recall task immediately ($p = 0.01$), and there was a trend for patients with epilepsy to recall fewer story units after a delay ($p = 0.024$).

Differences between patients with partial, generalized, and unclassified epilepsy

Fig. 2 plots the performance of patients with partial, generalized, and unclassified epilepsy across the neuropsychological test battery with the *x* axis representing the control mean. The pattern of performance is similar across the three groups. When one-way ANOVAs were conducted, the only task that demonstrated significant differences between the epilepsy groups was the motor speed task of the Adult Memory and Information Processing Battery ($F_{(3, 235)} = 7.441$, $p < 0.001$). Those with generalized epilepsy performed significantly worse than those with partial and unclassified epilepsy. However, these results should be interpreted with caution due to the unequal numbers in the groups.

Impact of previous seizure activity

Because a large proportion of patients had experienced several seizures before enrollment, correlational analyses were carried out to investigate the relationship between neuropsychological test performance and previous seizure activity. There were no relationships between the total numbers of seizures, the total number of generalized tonic–clonic seizures (including both primary and secondary generalized), and any of the cognitive measures.

Impact of mood

On the Profile of Mood States, patients with epilepsy reported experiencing significantly more symptoms of tension ($p < 0.001$), confusion ($p < 0.001$), and significantly less vigor ($p = 0.001$) than healthy volunteers. There were no relationships between the adjusted *z*-scores and the mood factors, suggesting the differences found on the neuropsychological tests are not mediated by mood disturbances.

Impairment index

The adjusted *z*-scores were used to identify individuals who demonstrated abnormal performance across the test battery. An adjusted *z*-score of ≤ -2.0 was used as a marker of abnormality. Fig. 3 illustrates the percentage of patients with epilepsy and healthy volunteers who had abnormal scores for each test. A higher proportion of patients with epilepsy had abnormal test scores compared with healthy volunteers for the majority of measures. This is particularly evident for those that assess memory and psychomotor speed.

Table 3 illustrates the proportion of tests that were impaired for the patients with epilepsy and healthy volunteers when different criterions of abnormality were applied. Even when the more conservative value of >2 SD below the control mean was used, 53.5% of the patients with epilepsy had at least one abnormal score compared

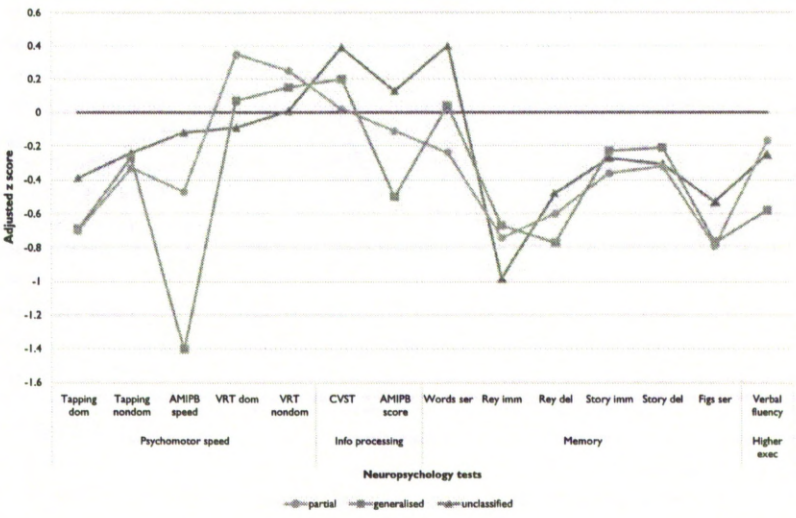

Figure 2.
Performance of patients with partial, generalized, and unclassified epilepsy across the neuropsychological test battery relative to healthy volunteers (straight line). *X* axis represents the mean performance of the healthy volunteers. Dom, dominant; nondom, nondominant; AMIPB, Adult Memory and Information Processing Battery; VRT, visual reaction time; CVST, Computerized Visual Search Task; ser, serial; imm, immediate; del, delayed.
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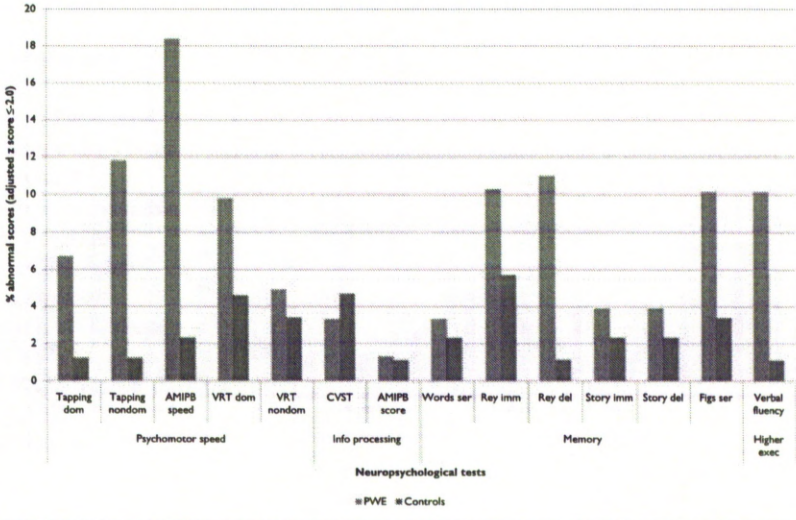

Figure 3.
Percentage of patients and healthy volunteers with abnormal scores [>2 standard deviation (SD) below the control mean] for each neuropsychological test variable. Dom, dominant; nondom, nondominant; AMIPB, Adult Memory and Information Processing Battery; VRT, visual reaction time; CVST, Computerized Visual Search Task; ser, serial; imm, immediate; del, delayed.
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with 20.7% of healthy volunteers. These individuals were classified as being impaired. Patients with epilepsy were significantly more likely to be in the impaired group compared with healthy volunteers [(χ^2 = 24.74, d.f. = 1, $p < 0.001$, odds ratio (OR) 4.42, 95% confidence interval (CI) 2.41, 8.11].

Characteristics of patients with epilepsy in the impaired group

There were no differences between those who were classified as impaired and those who were not in terms of sex ($p = 0.8.22$), age at assessment ($p = 0.980$), or education ($p = 0.192$). There were no differences between the two groups on any epilepsy-related variables. There were no differences in epilepsy type ($p = 0.155$), number of seizures at baseline ($p = 0.101$), or age at first seizure ($p = 0.542$), although there was a trend for those with a shorter interval since their first seizure to be in the impaired group ($p = 0.017$). There were no differences between the two groups on any of the mood variables.

Discussion

Cognitive impairments are frequently reported by people with epilepsy, but when these cognitive impairments arise in the course of the disease is an important issue.

Table 3. The proportion of tests impaired for patients and healthy volunteers across test battery

	>2 SD		>1.5 SD	
Proportion of tests impaired (%)	PWE (n, %)	Controls (n, %)	PWE (n, %)	Controls (n, %)
0	72 (46.5)	69 (79.3)	39 (25.2)	45 (51.7)
≥1	83 (53.5)	18 (20.7)	116 (74.8)	42 (48.3)
≥25	15 (9.7)	2 (2.3)	38 (24.5)	9 (10.3)
≥50	1 (0.6)	0 (0.0)	11 (7.1)	1 (1.1)

PWE, patients with epilepsy.

Many patients attribute their impairments to the side-effects of AED treatment (Carpay et al., 2005). However, the results of this study suggest that patients with newly diagnosed epilepsy, who are otherwise neurologically normal, were performing significantly worse than healthy volunteers on 10 of 16 cognitive measures before the start of treatment with AEDs. After adjusting for age, sex, and education, these differences persisted for the domains of memory and psychomotor speed. At an individual level, patients with epilepsy had a higher proportion of abnormal test scores (adjusted z-score ≤ -2.0) across the test battery and were four times more likely than healthy volunteers to demonstrate cognitive impairment (at least one abnormal test score).

Previous research has suggested that patients with newly diagnosed epilepsy already demonstrate evidence of cognitive dysfunction, in particular memory dysfunction, at the time of diagnosis (Smith et al., 1987; Kälviäinen et al., 1992; Äikiä et al., 1995; Prevey et al., 1998; Pulliainen et al., 2000a; Äikiä et al., 2001). Our study, consistent with these, has shown that impairments, particularly in memory functioning, occur in patients without structural brain abnormalities on clinical MRI, following few seizures and before AED treatment.

The observed differences were not mediated by the type or frequency of seizure activity. There were no differences between those with partial, generalized, and unclassified epilepsy, except for the motor speed task of the Adult Memory and Information Processing Battery. This supports Pulliainen et al. (2000a) but not Prevey et al. (1998), who found greater impairments in those with secondarily generalized seizures. However, our results must be interpreted with caution due to the unequal numbers in the groups. There were no relationships between the total number of seizures or the total number of generalized tonic–clonic seizures before the baseline assessment and any of the neuropsychological test variables. Epilepsy-related variables also did not explain the differences between those patients who were classified as impaired based on the impairment index, although there was a trend for those with more recent onset of first seizure to be in the impaired group.

The mechanisms underlying the cognitive impairments observed at the time of diagnosis are unclear. Some studies have suggested that it may be the result of epileptogenesis (Hermann et al., 2006). Studies in children with new-onset idiopathic and cryptogenic epilepsy have also shown generalized cognitive dysfunction at the time of diagnosis compared with healthy volunteers (Oostrom et al., 2003; Hermann et al., 2006). Some studies have found that behavior and academic problems in children antedate the first recognized seizure (Austin et al., 2001; Berg et al., 2005). However, the factors that cause some patients to be more susceptible to impairments than others remain to be determined.

Alternatively, patients were assessed at the time of diagnosis, which is a period of complex psychological adjustment (Velissaris et al., 2007). It may be that those who demonstrate the most dysfunction have a more pervasive loss of control and have a more extensive adjustment process (Velissaris et al., 2007). Oostrom et al. (2003) found that differences in cognitive functioning between children with newly diagnosed epilepsy and control children were not related to epilepsy characteristics but to the reaction of the child and their parent(s) to the diagnosis of epilepsy. By following up patients after 3 and 12 months, we will be able to see whether these deficits persist or improve with time and adjustment to the condition.

Equally, anxiety or depression may have affected patient's performance, as they were assessed at or near the time of diagnosis. There were differences between the current mood state of patients with epilepsy and healthy volunteers. Consistent with previous literature (Kanner, 2007), patients with epilepsy reported experiencing more mood disturbance, in particular, more symptoms of tension and confusion and less vigor than healthy volunteers. However, similar to the study by Pulliainen et al. (2000b), we found no relationship between the neuropsychological test variables and current mood state. Furthermore, in order to limit the impact of anxiety on test performance, psychometrists administering the neuropsychological tests were trained to postpone the assessment in any patient who demonstrated significant levels of distress based on clinical judgement.

There are limitations to this study. First, a better control group would have been family members of the patients with epilepsy to ensure similar sociodemographic backgrounds. However, because of limited resources (time and

financial) this was not possible. However, the healthy volunteers were equated for age and sex, although, they did have higher levels of education. Education is significantly correlated with age and IQ (Smith et al., 1987), so we adjusted for the effects of education in our analysis. Second, we did not formally assess the psychological reaction and adjustment to the diagnosis of epilepsy, which may be a possible explanation for the observed differences between patients and healthy volunteers. However, in our study, current mood, including symptoms of anxiety and confusion, were not related to cognitive test performance. Third, the effects of epilepsy syndrome could not be investigated due to the small numbers in each group. With larger numbers, it would be interesting to investigate the cognitive profiles of different epilepsy syndromes at the time of diagnosis. Finally, patients with abnormal neuroimaging on clinical computed tomography (CT)/MRI were excluded from the analysis to assess the impact of seizures and not the impact of underlying brain pathology on neuropsychological functioning. Future research needs to investigate whether potential structural or functional abnormalities underlie these deficits.

This cohort forms part of a longitudinal study investigating the natural history of cognitive functioning in people with newly diagnosed epilepsy. A proportion of these patients have now been followed up after 5 years, and this will form the basis of a further publication. A recent study has identified three different cognitive phenotypes in patients with temporal lobe epilepsy, and it has been suggested that these three subgroups follow a different cognitive course over a 4-year period (Hermann et al., 2007). It has also been suggested that those with cognitive dysfunction at the time of diagnosis are those who go on to develop intractable chronic epilepsy (Kälviäinen et al., 1992; Äikiä et al., 1995). We hypothesize that our group of patients who demonstrated cognitive dysfunction at the time of diagnosis may also have cognitive trajectories different from those who did not demonstrate dysfunction, will experience greater cognitive decline, and may be at risk of developing more severe intractable epilepsy.

There is a need to identify those patients already at risk of cognitive impairments so they can be referred for appropriate intervention and management to try and prevent further decline. Therefore, future research needs to focus on the characteristics of those patients who appear to be more susceptible to cognitive impairments, examine the mechanisms that may underlie their increased susceptibility, and assess the impact of seizures and treatment on an already compromised brain.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of patients with epilepsy and healthy volunteers.

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Newly diagnosed epilepsy: Cognitive outcome at 5 years

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ABSTRACT

Many people with epilepsy experience cognitive problems as a consequence of their epilepsy and its treatment. However, relatively few longitudinal studies have been conducted to investigate how these problems progress during the course of the disorder, particularly in those who are newly diagnosed. Fifty patients with newly diagnosed epilepsy were assessed using a comprehensive neuropsychological test battery before they started antiepileptic treatment and after a mean of 5 years. At the 5-year follow-up, the majority of cognitive measures remained stable, although significant (but subtle) declines were noted for memory and psychomotor speed domains in 38% of people with epilepsy.

1. Introduction

People with epilepsy (PWE) are at risk of developing cognitive dysfunction. The causes of cognitive impairments in PWE are thought to be multifactorial. The main factors include the effects of the underlying etiology, the effects of recurrent seizures, the side effects of antiepileptic drug (AED) treatment, and psychosocial issues [1–4]. The majority of research has focused on the nature and cause of these impairments, in particular the cognitive side effects of AED treatment; however, there is increasing interest in determining how these problems progress during the course of the disorder.

Although a number of cross-sectional studies have suggested that cognitive functioning declines with increasing duration of epilepsy [5–10], others have not found evidence of deterioration over time [11,12]. Even though cross-sectional studies are useful in studying the relationships between cognition and long duration of epilepsy in large samples of patients, they have several limitations (e.g., cause and effect and undetected cohort bias effects). Therefore, a more appropriate approach to answering this type of question is a longitudinal design.

Comparatively few longitudinal studies have been conducted in adults with epilepsy. Two recent reviews have identified all published longitudinal studies [13,14]. Similar to the findings from cross-sectional studies, the results are mixed. Some have suggested that as a group, PWE decline in areas of functioning, particularly in memory, attention, executive control, speed of response, and visual–spatial relations [15–22]. However, there is variability in cognitive outcome. Helmstaedter et al. [17] identified 37% of patients with temporal lobe epilepsy (TLE) who declined in memory functioning; Arieff and Yacorzynski [15] also identified 37% who significantly decreased in intellectual functioning, and Hermann et al. [21] identified 20–25% who had adverse cognitive outcomes. In contrast, several studies have suggested either improvements or general stable functioning over time [16,23–31]. These mixed findings probably reflect their differing methodologies. The studies have varied in their test–retest intervals, the cognitive domains studied, neuropsychological tests used, and types of patients assessed.

In addition, the majority of these studies have included those with severe, chronic intractable epilepsy and often of long duration. Only two studies have included those with newly diagnosed epilepsy [27,28]. One was a published abstract from a study following 58 patients with newly diagnosed partial epilepsy over 5 years. There were no significant declines across a comprehensive neuropsychological test battery [27]. The second study [28] presented only preliminary data on verbal intellectual and verbal memory functioning in 20 patients with newly diagnosed TLE. There were also no significant declines after 5 years. Therefore, in comparison to those with chronic, long-standing epilepsy, very little is known about the cognitive functioning of adults with new-onset epilepsy. This study aimed to document the longer-term effects of epilepsy and its treatment on cognitive functioning in adults with newly diagnosed epilepsy by following up patients who were involved in the Standard and New Antiepileptic Drugs (SANAD) Neuropsychology study 3 to 8 years after their diagnosis [32].

2. Methods

This study included PWE who were involved in the SANAD trial. SANAD was a pragmatic, multicenter, randomized, unblinded, parallel

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group clinical trial comparing the clinical and cost effectiveness of standard (carbamazepine or valproate) and new (gabapentin, lamotrigine, oxcarbazepine, topiramate) AEDs. A full description of the study methods has been given elsewhere [33,34]. At the time of randomization into SANAD, newly diagnosed adults (aged >15 years) who were previously untreated from 10 of the hospital centers (most active recruiting centers) were invited to take part in the SANAD Neuropsychology study. The study methods have been described in [32]. Briefly, 222 PWE were assessed before the start of AED treatment using a comprehensive battery of neuropsychological tests. Baseline assessments were undertaken between October 2000 and August 2004. They were then reassessed after 3 and 12 months of treatment. A total of 147 PWE were assessed at 12 months.

2.1. SANAD Neuropsychology follow-up study

Those who had completed all three assessments as part of the SANAD Neuropsychology study were invited to take part in a neuropsychology follow-up assessment. PWE were approached to take part in the follow-up study if they had completed the 12-month assessment as part of the SANAD Neuropsychology study; they still had a diagnosis of epilepsy, and they gave informed consent. PWE were excluded from taking part if they had undergone epilepsy surgery or they had expressed a wish not to take part in any further research as part of SANAD. Eligibility was checked with the clinical information obtained as part of SANAD and by asking patients about their medical history informally in a semistructured interview prior to the assessment.

Patients were recruited between November 2007 and November 2008 and assessed using the same comprehensive battery of tests as in the SANAD Neuropsychology study. A semistructured interview was also conducted to obtain up-to-date demographic and clinical information. This included: current medication, seizure frequency or period of seizure freedom, occurrence of any other medical or psychological problems since the 12-month assessment, and socio-demographic characteristics such as employment status and educational history.

Both the SANAD Neuropsychology study and the follow-up study received ethical approval from the North West Research Ethics Committee and local research governance approval. All participants gave written informed consent.

2.2. Neuropsychological test battery

The neuropsychological test battery comprised measures from the FePsy computerized test program [35] as well as traditional paper-and-pencil measures (see Table 1). The test battery was aimed at assessing a wide variety of cognitive domains. Each of the tests was selected on the basis of its proven reliability, validity, and use in people with epilepsy [36,37]. The battery took approximately 1½ hours to complete. The tests were administered in a fixed order to ensure adequate time passed to test delayed recall on the memory tasks. However, regular breaks were offered and taken to reduce fatigue effects. Neuropsychological assessment was postponed to a later date for those patients who reported having a seizure within 24 hours of the assessment. Parallel, alternate forms were used, where available, in the follow-up sessions to reduce practice effects associated with repeat neuropsychological testing [38].

Table 1
Neuropsychological test battery.

Domain	Test	Outcome variable
Psychomotor speed	Finger tapping	Average number of taps for the dominant and nondominant hand across five trials
	Visual reaction time	Average reaction time (ms) for the dominant and nondominant hand
	AMIPB[a] psychomotor speed	Mean number of digits crossed through over two trials
Memory	Recognition of words/figures	Number of words or figures correctly answered on the serial/simultaneous version of the task
	Rey Auditory Verbal Learning Task	Sum of words recalled over the five trials and number of words recalled after a 30-min delay
	Story recall	Number of story units recalled immediately and after a 10-min delay
Information processing	AMIPB information processing	Mean number of correct responses over the two tasks
	Binary choice reaction time	Average response speed (ms)
	Computerized Visual Search Task	Average speed of response (s)
Mental flexibility	Stroop	Number of correct responses on the color–word task
	Benton verbal fluency	Total number of acceptable words produced
Mood	Profile of Mood States	Transformed scores (per 100) for each mood factor
Subjective report of cognitive complaints	Aldenkamp–Baker Neuropsychological Assessment Schedule	Transformed scores (per 100) for each subscale

[a] AMIPB, Adult Memory and Information Processing Battery.

2.3. Statistical analysis

Data were analyzed using SPSS (Version 16.0). Independent *t* tests and χ^2 analysis were used to examine differences in demographic, clinical, and neuropsychological characteristics between those who did and those who did not participate in the follow-up assessment. Differences between baseline and follow-up neuropsychological test scores at a group level were examined using dependent *t* or Wilcoxon signed-rank tests, depending on whether scores were normally or nonnormally distributed. Because of the low ceiling observed on the Stroop color–word test, this was converted to a categorical variable based on normative data [39]. Descriptive statistics were used to describe the proportion of people in each category (borderline, low average, average). Percentage change scores were calculated and transformed so that for all tests, positive values indicated improvement from baseline and negative values indicated decline from baseline. Separate exploratory analyses (e.g., Spearman correlations, Mann–Whitney, and Kruskal–Wallis tests) were conducted to assess variables that might influence cognitive change. These independent variables were either analyzed as continuous variables or transformed into dichotomous ones. The independent variables were: seizure freedom for at least the previous 12 months (yes/no), age, years of education, duration of epilepsy, presence of comorbidities at follow-up (yes/no), and Tension–Anxiety factor from the Profile of Mood States (POMS).

To assess cognitive change at an individual level and evaluate the clinical significance of results, the proportion of patients who had experienced cognitive decline was calculated. This was calculated relative to the cross-sectional SD of the relevant baseline scores [40–42]. Cognitive decline was defined as a decline of more than 2SD on any of the neuropsychological tests. Some studies have used less conservative values of ≥1SD to define decline [e.g., 41]. However, several previous studies have also defined cognitive decline using the more conservative values above [e.g., 19]. The more conservative values were chosen so as not to overestimate the number of patients who were classified as experiencing cognitive decline, especially as evaluating change using this SD method has been found to overclassify deterioration in test performance compared with other

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methods (e.g., reliable change indices and regression-based models) [42]. An exploratory analysis, using independent *t*, Mann–Whitney, and χ^2 tests, was conducted to identify the demographic and clinical characteristics of those who were identified as having cognitive decline. Because of the number of multiple comparisons being made, a Bonferroni correction was applied, setting the significance level for the inferential statistics as $P<0.01$.

3. Results

3.1. Response rate

A total of 147 PWE had completed all three assessments; of these, 132 were eligible for the follow-up study (reasons for noneligibility: 7 patients had died, 3 were from the two centers that did not participate in the follow-up study, 2 requested not to take part in future research, 2 did not have up-to-date contact details, 1 had undergone epilepsy surgery). Of the 132 who were invited to undergo a follow-up assessment, 54 (41%) responded positively, 37 (28%) declined, and 41 (31%) did not respond to the invitation letter. Reasons for not wanting to take part included: ill health ($n=3$), did not feel that they had the time ($n=2$), family or work commitments ($n=4$), tired of taking part in research ($n=1$), no longer had epilepsy so did not want to contribute; ($n=1$) 26 did not provide a reason. Of the 54 who wanted to take part, 50 completed the follow-up assessment. Assessments were not completed for 4 patients for various reasons: frequency and severity of seizures made it too difficult to carry out an accurate assessment for one patient; one canceled and did not want to rearrange; and after responding to the initial invitation letter, two patients could not be contacted to arrange an assessment time.

3.2. Clinical and demographic characteristics

As outlined in Table 2, the majority of participants were females with an average age of 46 years (range: 21–84). It had been a mean of 64 months since their baseline assessment (range: 43–85). This test–retest interval is used as a surrogate for duration of epilepsy, as these patients were newly diagnosed at the time of the baseline assessment. There were no differences in terms of age at baseline ($t[130]=-1.11$, $P=0.267$) or gender ($\chi^2[1]=2.184$, $P=0.139$) between those who did and those who did not take part in this follow-up study. The majority had partial epilepsy. There were no differences in baseline seizure type between those who did and those who did not take part ($\chi^2[2]=4.574$, $P=0.102$). The majority had been seizure free for at least the 12 months prior to the assessment.

Eighty percent were on monotherapy at follow-up. Lamotrigine (20%), carbamazepine (18%), and topiramate (18%) were the most commonly prescribed drugs. Eight (16%) were treated with polytherapy on six different combinations (three carbamazepine and levetiracetam, one carbamazepine and topiramate, one lamotrigine and valproate, one lamotrigine and clobazam, one levetiracetam and clobazam, and one topiramate and pregabalin).

Forty percent of those who took part in the follow-up assessment reported experiencing other medical conditions (e.g., cancer, diabetes, gynecological problems) unrelated to their epilepsy since their 12-month assessment. Previous psychological problems were reported by five participants, four of whom had sought treatment (three for depression, one for anger management). Of those who had reported experiencing psychological problems since the 12-month assessment, none reported still experiencing them at the time of the follow-up assessment.

At the time of follow-up, just over half were in paid employment or full-time education. They had a median of 12 years of education, and 82% had achieved formal educational qualifications. Forty-four percent had achieved school-level qualifications (GSCEs/CSEs or equivalent) and 30% had achieved the equivalent of A-levels or higher (postschool qualifications). They had significantly more years of formal education at baseline than those who were eligible but did not take part in the follow-up study ($\chi^2[2]=11.30$, $P=0.004$). However, there were no differences between the two groups on any of the baseline neuropsychological measures, although there was a trend for those who did not take part to have lower scores on both aspects of the Adult Memory and Information Processing Battery (AMIPB information processing $t[130]=-2.36$, $P=0.020$; AMIPB psychomotor speed $t[125]=-2.13$, $P=0.035$). Similarly, there were no differences between the two groups on any of the 12-month neuropsychological measures.

Table 2
Clinical and demographic characteristics of PWE ($n=50$).

Sex	
Male	19 (38.0%)[a]
Female	31 (62.0%)
Mean age at baseline	41.34 (15.01) [15–78]
Mean age at follow-up	46.76 (15.22) [21–84]
Mean test–retest interval, months	64.24 (10.75) [43–85]
Seizure type at baseline	
Partial	42 (84.0%)
Generalized	4 (8.0%)
Unclassified	4 (8.0%)
Seizure frequency at follow-up	
None	29 (58.0%)
Daily	3 (6.0%)
Weekly	3 (6.0%)
Monthly	12 (24.0%)
Yearly	3 (6.0%)
Seizure free in preceding 12 months	29 (58.0%)
Other comorbidities	20 (40.0%)
Employment status at follow-up	
In paid full/part-time work	25 (50.0%)
In full-time education	1 (2.0%)
Retired	9 (18.0%)
Unemployed	15 (30.0%)
Median years of education at follow-up, (25th–75th centiles)	12 [11–16]
Highest qualification obtained at follow-up	
None	9 (18.0%)
Other	2 (4.0%)
GCSE/CSE or equivalent[b]	22 (44.0%)
A-levels or equivalent[b]	4 (8.0%)
Diploma	4 (8.0%)
Degree or higher	9 (18.0%)

[a] Values are expressed as *n* (%) or mean (SD) [range].
[b] GCSE/CSE or equivalent are school-level qualifications (11–16 years); A-levels or equivalent are post-16 qualifications.

3.3. Changes in neuropsychological functioning

As outlined in Table 3, PWE had statistically significantly slower reaction times at follow-up on the visual reaction time task with both the dominant hand and nondominant hand compared with baseline. They also had significantly lower scores at follow-up compared with baseline on the immediate and delayed tasks of the Rey Auditory Verbal Learning Test (AVLT). There were also trends for worse performance at follow-up on serial recognition of words, the information processing task of the AMIPB, and the Computerized Visual Search Task (CVST). However, there was a trend toward improved performance on the serial recognition of figures task. A larger proportion of patients were performing in the average range at follow-up compared with baseline on the Stroop Color–Word task (71.7% vs 66.7%). Fewer patients were performing in the borderline range at follow-up compared with baseline (15.2% vs 16.7%). This suggests that, as a group, patients improved over time on this task.

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Table 3
Changes in neuropsychological test variables from baseline to follow-up.

Variable	Baseline	Follow-up	Difference (95% CI)	*P* value
Finger tapping				
Dominant	56.02 (9.75) [48][a]	56.34 (9.23) [48][a]	−0.32(−3.42, 2.78)	0.836
Nondominant	51.34 (8.57) [47]	50.43 (6.70) [47]	0.90 (−1.46, 3.26)	0.446
Visual RT (ms)[b]				
Dominant	309.37 (62.97) [46]	348.13 (54.00) [46]	−38.76 (−59.04, −18.48)	<0.001[c]
Nondominant	311.98 (68.84) [48]	366.33 (68.07) [48]	−54.35 (−73.82, −34.89)	<0.001[c]
Binary choice RT (ms)[b]	341.00 (308.00–424.00) [45]	361.00 (313.00–419.00) [45]	−7 (−27, −16)	0.519
CVST (s)[b]	10.80 (4.10) [46]	11.87 (3.60) [46]	−1.06 (−2.00, −0.13)	0.027[d]
Word recognition				
Serial	15.94 (4.11) [47]	14.23 (4.75) [47]	1.70 (0.24, 3.16)	0.023[d]
Simultaneous	20.00 (17.00–22.00) [43]	19.00 (17.00–21.00) [43]	0.5 (−0.5, 1.5)	0.249
Figure recognition				
Serial	14.29 (4.00) [45]	15.56 (4.65) [45]	−1.27 (−2.49, −0.04)	0.043[d]
Story recall				
Immediate	8.34 (2.64) [50]	7.89 (2.73) [50]	0.45 (−0.24, 1.14)	0.197
Delayed	7.20 (2.62) [50]	7.39 (2.88) [50]	−0.19(−0.90, 0.52)	0.593
Rey AVLT				
Immediate	45.88 (9.16) [50]	40.34 (10.79) [50]	5.54 (2.70, 8.38)	<0.001[c]
Delayed	10.00 (7.00–11.00) [50]	8.00 (6.00–10.00) [50]	−1.5 (−2, −1)	0.001[c]
Verbal fluency	35.90 (12.48) [50]	35.78 (12.68) [50]	0.12 (−2.69, 2.93)	0.932
AMIPB				
Information processing	63.39 (16.33) [50]	59.80 (18.49) [50]	3.59 (0.81, 6.37)	0.012[d]
Psychomotor speed	48.65 (10.91) [49]	46.71 (9.07) [49]	1.94 (−0.82, 4.70)	0.164

[a] Values are expressed as the mean (SD) [*n*] or median (25th–75th percentiles) [*n*].
[b] Higher score means worse performance.
[c] $P<0.001$.
[d] $P<0.05$.

In terms of mood, PWE reported feeling significantly fewer symptoms of tension at the follow-up assessment ($t[49]=3.00$, $P=0.004$). There were no statistically significant changes in any of the other mood factors of the POMS. There were no statistically significant changes on the Aldenkamp–Baker Neuropsychological Assessment Schedule (ABNAS), although patients reported experiencing more memory, language, and concentration problems and cognitive slowing at the follow-up assessment.

3.4. Percentage change

Fig. 1 plots the median percentage change scores across the neuropsychological test battery. The tests with the most decline from baseline are the delayed subtest of the Rey AVLT, visual reaction time with the dominant hand and nondominant hand, and the CVST, consistent with the results of the dependent *t* tests. The declines are subtle, and scores on most measures on average declined less than 5% from baseline. The Rey AVLT and visual reaction time tasks seem to have been the most vulnerable at follow-up, with an average decline from 17% from baseline for the Rey AVLT. Interestingly, improvements were found on the story recall tasks and serial recognition of figures.

3.5. Factors associated with cognitive change

There were no differences in percentage change scores between those who had been and those who had not been seizure free in the preceding year, between those with daily/weekly/monthly seizures and those with yearly seizures, and between those with comorbid diagnoses and those without comorbid diagnoses for any cognitive measure. There was a trend for years of education to be significantly positively associated with percentage change on the delayed story recall task ($r_s=0.316$, $P=0.025$) and duration of epilepsy to be significantly negatively associated with simultaneous recognition of words ($r_s=-0.326$, $P=0.033$). Age at the time of follow-up assessment was significantly negatively associated with psychomotor speed subtests of the AMIPB ($r_s=-0.442$, $P=0.001$) and exhibited trends with the information processing subtest ($r_s=-0.321$, $P=0.023$) and serial recognition of words ($r_s=-0.297$, $P=0.042$). Scores on the Tension–Anxiety factor of the POMS were significantly negatively associated with tapping with the dominant ($r_s=-0.527$, $P<0.001$) and nondominant ($r_s=-0.383$, $P=0.008$) hand and the psychomotor speed subtest of the AMIPB ($r_s=-0.385$, $P=0.006$), and there was a trend with delayed recall ($r_s=-0.282$, $P=0.047$) on the Rey AVLT.

3.6. Individual change

Thirty-eight percent of patients were classified as experiencing cognitive decline. An exploratory data analysis was conducted to investigate the clinical and demographic characteristics of those who were classified as having cognitive decline compared with those who were not so classified. There were no significant differences between the two groups on any of the demographic, psychological, or epilepsy-related variables (see Table 4).

4. Discussion

This study investigated the longer-term impact of epilepsy and its treatment on cognition in newly diagnosed people with epilepsy. The results indicate that after a mean of 5 years since diagnosis, the majority of cognitive measures remained stable but there were statistically significant declines in 4 of the 16 measures. Measures affected were those assessing psychomotor speed and verbal memory. However, the magnitude of this change was subtle, 10–15% from baseline. Cognitive changes, particularly for psychomotor speed measures, were most associated with higher levels of tension. Older age was also significantly associated with poorer performance on a measure of psychomotor speed. At an individual level, 38% of patients were classified as experiencing cognitive decline (i.e., at least one cognitive test score >2SD below baseline).

The relatively stable findings for the majority of measures support some of the previous work in this area [16,24–28,31], but must be interpreted with caution because of the lack of a control group. This has been identified as a methodological shortfall of previous studies of this type, as the neuropsychological test performance of PWE has been characterized by "abnormal" functioning rather than abject

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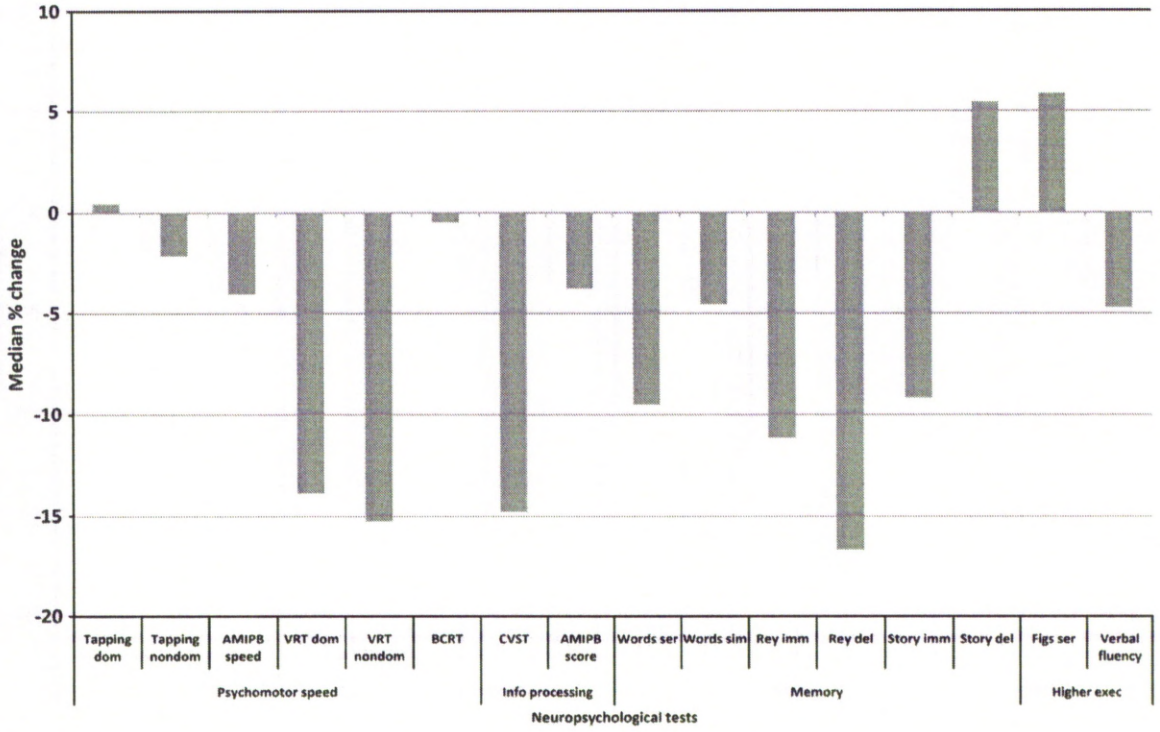

Fig. 1. Median percentage change score across the neuropsychological test battery. dom, dominant; nondom, nondominant; AMIPB, Adult Memory and Information Processing Battery; ser, serial; imm, immediate; del, delayed; exec, executive.

deterioration [14,43]. To date, there have only been five controlled longitudinal studies, and these have arrived at conclusions different from those of studies that did not employ a control group. These studies have indicated that compared with healthy volunteers, PWE have different cognitive trajectories, which are characterized by a lack of practice effects [19,21,22,30,31]. Therefore, this study cannot make conclusions in comparison to "normal" performance, but the lack of improvement despite prior exposure to the tests at baseline, 3 months, and 12 months lends support to this hypothesis.

The finding of declines on some measures, particularly those assessing verbal memory, is congruent with several previous longitudinal studies [15,17,18,20–22], but is inconsistent with studies involving newly diagnosed PWE [27,28]. Aikia and colleagues reported no significant declines on measures of verbal ability, verbal learning and memory, attention, and flexibility of mental processing after 5 years. They also found statistically significant (although small) improvements in several neuropsychological measures as a result of normal practice effects, although they did not report which measures improved [27]. In their later study, there was no deterioration and some improvement (delayed recall of a list learning task) in verbal memory in 20 adults with newly diagnosed TLE. The differences may possibly be explained by the demographic and clinical characteristics of the PWE in the studies (e.g., all participants were seizure free in [27]; there may be differences in AED treatment—20% were taking topiramate in our study, which is a known risk factor for cognitive impairment [44–49]; and there may have been differences in age, education, and type of epilepsy).

The finding that higher levels of tension were associated with declines in measures of psychomotor speed (finger tapping task and the psychomotor speed task of the AMIPB) is consistent with previous research that has suggested that mood disturbance may interfere with performance on neuropsychological tests, particularly timed tasks [50–52]. Older age was also associated with poorer performance on the AMIPB psychomotor speed task; this association has previously been reported [53]. However, there were no differences in self-reported symptoms of anxiety or age between those who were and those who were not classified as having cognitive decline. The fact that this study failed to identify any factors that differentiated those who were and those who were not classified as experiencing cognitive decline is interesting. Possibly the definition of abnormal test performance employed in this study is too lenient; PWE may not differ on these factors but on some other indicator that was not measured (e.g., functional/structural neuroabnormalities identified from EEG and/or imaging data). Or it may reflect the heterogeneity of the sample. However, the proportion of PWE experiencing epilepsy is in concordance with other longitudinal studies investigating cognitive change in PWE [15,18,24].

4.1. Limitations of the study

There are limitations to this work. First, as discussed above, the lack of a control group at follow-up means that the results need to be interpreted with caution. Second, the PWE in this study represent a heterogeneous group with different etiologies, seizure types, and syndromes. Different syndromes have been associated with different types of deficits [54,55]. A potential avenue for future research would be to recruit participants with specific syndromes at the time of diagnosis and follow these more homogenous groups over the course of the disorder. Third, selection bias may have occurred at follow-up. There was a large loss to follow-up. Only 23% of the original sample from the SANAD Neuropsychology study was involved in the follow-up assessment, and only 38% of those approached participated. Those who remained in the study may have been those who were concerned about cognitive problems and wanted a neuropsychological assessment, or those who felt that their epilepsy did not have a significant impact on their cognitive functioning may not have felt that the study was relevant to them and dropped out. Equally, those who found the neuropsychological tasks most challenging, or were most impaired,

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Table 4
Characteristics of those classified as having or not having cognitive decline at follow-up.

Characteristic	Declined ($n=19$)	Not declined ($n=31$)	Difference (95%CI)	*P* value
Sex				
Male	7 (36.8%)[a]	12 (38.7%)	−1.9(−27.9, 25.9)	0.895
Female	12 (63.2%)	19 (61.3%)	1.9 (−25.9, 27.9)	
Age at follow-up, years	51.11 (14.17) [22–84]	44.10 (15.45) [21–71]	7.01 (−1.77, 15.79)	0.115
Age at baseline, years	45.84 (13.89) [17-78]	38.58 (15.21) [17-65]	7.26 (−1.37, 15.89)	0.097
Duration, months	62.21 (11.23) [43-85]	65.48 (10.43) [46-84]	−3.27 (−9.56, 3.02)	0.301
Seizure type at baseline				
Partial	15 (78.9%)	27 (87.1%)	−8.1 (−32.7, 12.7)	NA[b]
Generalized	1 (5.3%)	3 (9.7%)	−4.4 (−21, 16.4)	
Unclassified	3 (15.8%)	1 (3.2%)	12.6 (−3.5, 35.1)	
Seizure free in preceding 12 months	13 (68.4%)	16 (51.6%)	16.8 (−11.7, 41.7)	0.242
Number of AEDs at follow-up				
0	0 (0%)	2 (6.5%)	−6.5 (20.9, 11.1)	NA[b]
1	15 (78.9%)	25 (80.6%)	−1.7 (−27.1, 20.3)	
2	4 (21.1%)	4 (12.9%)	8.1 (−12.7, 32.7)	
On topiramate at follow-up	5 (26.3%)	5 (16.1%)	10.2 (−12.4, 35.5)	0.382
Comorbidities at follow-up	8 (42.1%)	12 (38.7%)	3.4 (−23.5, 30.9)	0.812
Median education at follow-up, years (25th–75th centiles)	12 (11-18)	12 (11-15)	0 (−1, 2)	0.812
Median tension-anxiety at follow-up (25th–75th centiles)	30.56 (16.67-44.44)	22.22 (13.89-36.11)	−8.33 (−2.78, 19.44)	0.136
Employment status at follow-up				
Employed/full-time education	8 (42.1%)	18 (58.1%)	−16.0 (−41.9, 12.5)	0.273
Unemployed/retired	11 (57.9%)	13 (41.9%)	16.0 (−12.5, 41.9)	

[a] Values are expressed as *n* (%) or mean (SD) [range].
[b] Numbers in each cell are too small for tests of significance.

may not have wanted to take part. However, there were no differences on any of the baseline or 12-month cognitive measures, suggesting that they were representative of the original sample.

Despite these limitations, this study suggests that although cognitive function remains generally stable, some PWE may be at risk of experiencing cognitive decline, particularly in areas of verbal memory functioning. We feel this study provides important information on the neuropsychological progression of epilepsy in new-onset patients. Future work needs to concentrate on identifying the prognostic factors that predict those most at risk and to follow-up PWE for longer periods. In addition, PWE should be monitored, as part of their routine clinical management, for cognitive changes over time so that they can be referred for more comprehensive neuropsychological assessment and appropriate intervention.

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